ENB Therapeutics

OVERCOMING IMMUNOTHERAPY RESISTANCE

Two unique mechanisms that target the tumor microenvironment

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

NOVEMBER 18, 2019

Blazing a trail that benefits patients and investors

Potential First and Best-in-Class
Selective Inhibitors to reverse immunotherapy resistance

Strong and Broad IP
and Regulatory Exclusivity

Soon-to-be Announced collaboration
with big Pharma partner

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

Short-Term Milestones
IND filing 2Q 2019; PI/PII initiation 3Q 2019

Solid Leadership and Scientific Team
Scientific founders discovered the 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

ENB Therapeutics snapshot

Founded in 2015

- Focused on 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 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 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

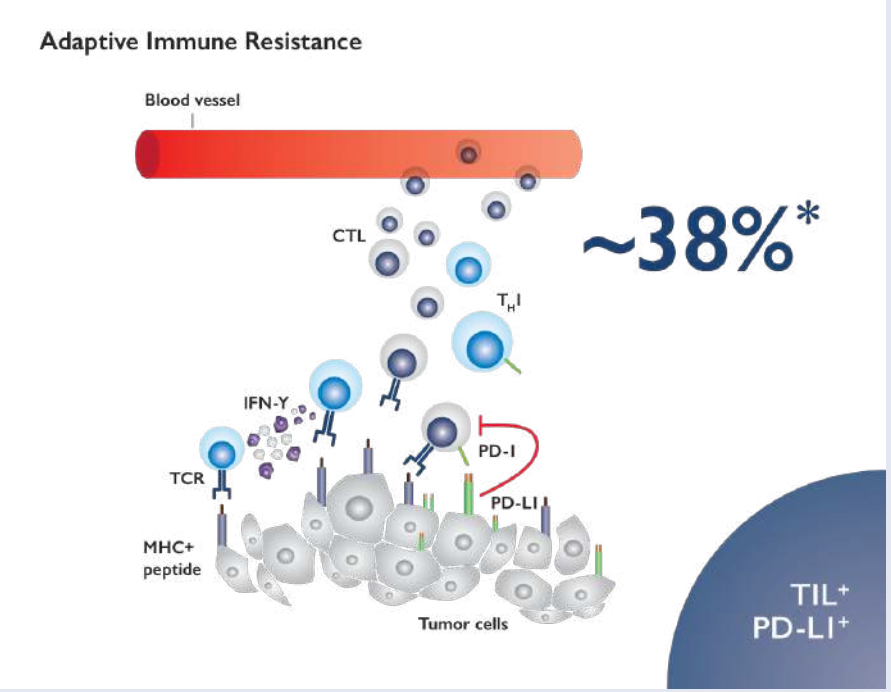
Consultants

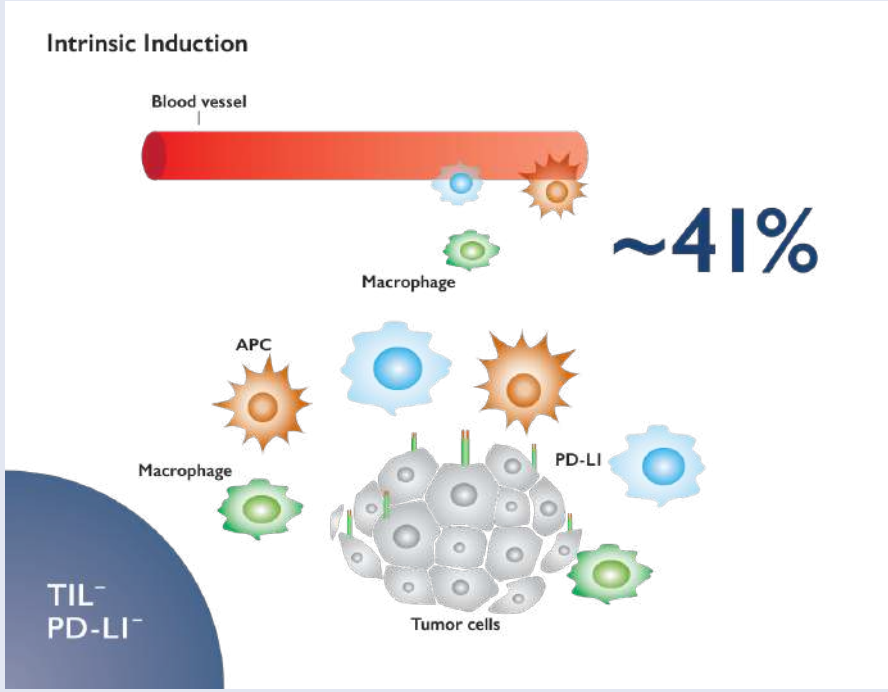
- CMC-**Vincent Bille, PhD**, Founder Marble Pharma Consulting, 1990-2007 UCB/Lonza, expertise in synthetic peptide manufacturing
- Safety/tox: **Rashmi Sharma, PhD,** Camargo Pharm. Svcs. 16+ years industry experience in pre-clincal IND enabling study direction and management

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**



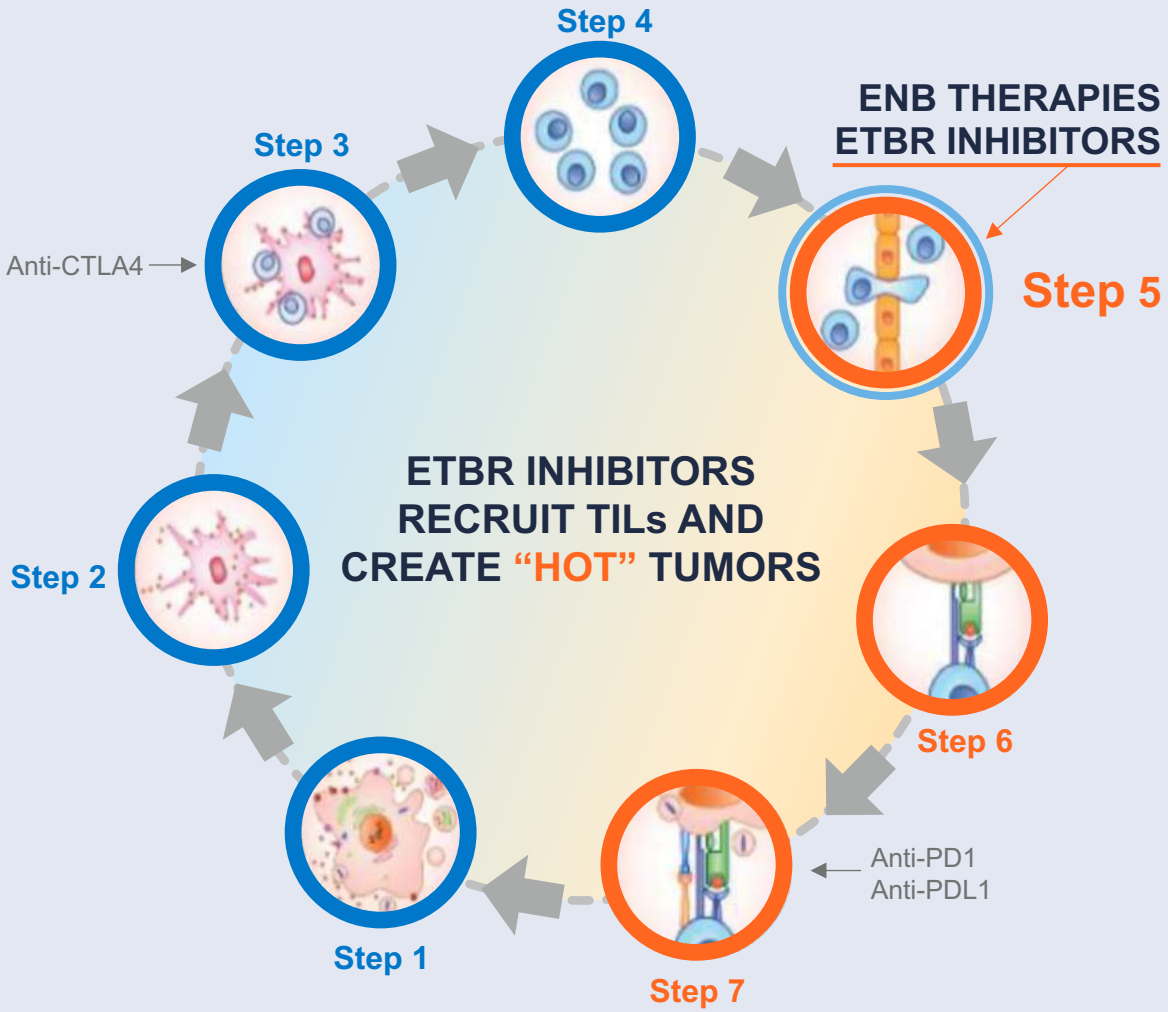


IO: Immunotherapy; **TIL:** Tumor infiltrating lymphocytes; **TME:** Tumor microenvironment

Source: Teng et al, *Cancer Research* 2015

Switching 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- 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
- 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 14)
  - → No B selective inhibitors have ever been tested in clinical trials for cancer

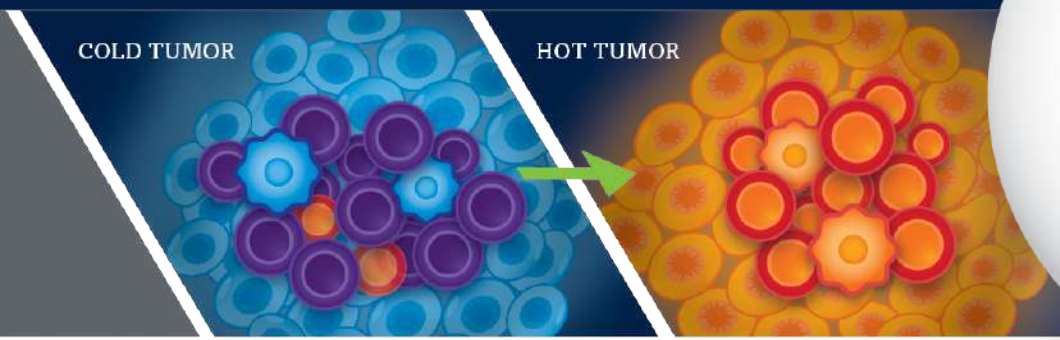


ETBR: endothelin B receptor

Overcoming IO resistance across multiple cancer types

Selective ETBR inhibition targets the TME through two unique mechanisms

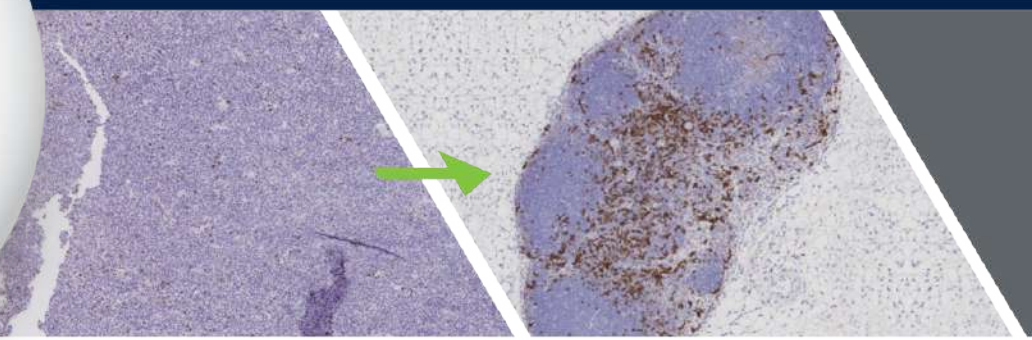
1. Switching immune-suppressed “cold” TMEs to “hot” TMEs, allowing TILs to infiltrate tumors



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

BQ788 (our parent compound) was originally developed as a research tool

- BQ788: small molecule developed at Merck/Banyu in 1994 as a research tool (never commercialized)
- Compound has been safely administered in many human clinical trials to investigate endothelin axis in cardiovascular system
  - Doses previously administered safely in humans are higher than anticipated therapeutic doses for cancer

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 4892–4896, May 1994
Medical Sciences

Biochemical and pharmacological profile of a potent and selective endothelin B-receptor antagonist, BQ-788

(receptor subtype)

KIYOFUMI ISHIKAWA*, MASAKI IHARA, KAZUHITO NOGUCHI, TOSHIAKI MASE, NOBUYUKI MINO, TOSHIHIKO SAEKI, TAKAHIRO FUKURODA, TAKEHIRO FUKAMI, SATOSHI OZAKI, TOSHIO NAGASE, MASARU NISHIKIBE, AND MITSUO YANO

New Drug Discovery Research Laboratories, Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Okubo 3, Tsukuba 300-33, Japan

Communicated by Edward M. Scolnick, January 28, 1994

ABSTRACT **We describe the characteristics of a potent and selective endothelin (ET) B-receptor antagonist, BQ-788 [*N-cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine]. *In vitro*, this compound potently and competitively inhibits ^{125}I-labeled endothelin 1 (ET-1) binding to ET_B receptors on human Girardi heart cells (IC_{50}, 1.2 nM) but only poorly inhibits the binding to ET_A receptors on human neuroblastoma cell line SK-N-MC cells (IC_{50}, 1300 nM). In isolated rabbit pulmonary arteries, BQ-788 shows no agonist activity up to 10 μM and competitively antagonizes the vasoconstriction induced by an ET_B-selective agonist, BQ-3020 (pA_2, 8.4). In rat, an ET_A-selective antagonist, BQ-123 (1 mg/kg, i.v.), does not affect transient depressor response to ET-1 (0.3 nmol/kg, i.v.) but potently inhibits following sustained pressor response; vice versa, BQ-788 (1 mg/kg, i.v.) abolishes the depressor response, resulting in a rapid onset of apparently enhanced pressor response. Thus, being a potent and selective ET_B receptor antagonist, BQ-788 may be considered as a powerful tool for investigating the role of ET in physiological and pathological processes.**

Endothelin 1 (ET-1) was first isolated from the culture supernatant of porcine aortic endothelial cells (1). The peptide is some 10-fold more potent than angiotensin II as a vasoconstrictor and has extremely long-lasting pressor effects (2). Subsequent studies, including human genomic analysis, identified two additional structurally and functionally related isopeptides named ET-2 and ET-3 (3).

ET receptors are widely distributed not only in vascular but also in nonvascular tissues (4, 5) and are classified into two subtypes termed ET_A (6–8) and ET_B (9–13) according to their distinctions in affinity for the ET isopeptides—i.e., the ET_A receptor has high affinity for ET-1 and ET-2 and relatively low affinity for ET-3, while the ET_B receptor has high affinity equally for all ET isopeptides.

ET_A receptors are predominantly found in peripheral tissues, especially in vascular smooth muscle tissues to mediate vasoconstriction, though they are also present in certain regions of the brain (6, 7). On the other hand, ET_B receptors have been thought to be exclusively localized to the endothelium and nonvascular tissues such as the liver, kidney, and brain (14). Endothelial ET_B receptors are functionally linked to vasodilation possibly through the release of endothelium-derived relaxing factor (15). However, it has now been confirmed that ET_B receptors are also located in certain vascular smooth muscle tissues, mediating vasoconstriction (16–19). Thus, the function of ET_B receptors is yet to be fully elucidated. In certain nonvascular tissues such as guinea pig bronchus and trachea, ET-1-induced constriction is also mediated by ET_B receptors (20–22). A recent *in vivo* study, using an ET_A antagonist, BQ-123 [*cyclo*(-D-Trp-D-Asp-Pro-D-Val-Leu-] (23, 24), and an ET_B agonist, [$Ala^{1,3,11,15}$]ET-1 (25), has demonstrated that bronchoconstrictor response as well as transient pressor response to ET-1 or ET-3 in guinea pigs is mediated by ET_B receptors, while sustained pressor response to ET-1 is mediated by ET_A receptors (26). As mentioned above, several subtype-selective ET ligands are now available and undoubtedly useful in elucidating the physiological and pathological roles of the ETs and their receptor subtypes. Of these selective ligands, only one, IRL 1038, has been reported as an ET_B antagonist (21).

We previously reported on a series of potent tripeptide ET_A antagonists, which were identified through systematic and extensive modification of a new lead tripeptide, *N*-isovalerylL-L-leucyl-D-tryptophanyl-β-alanine, designed on the basis of a structure–activity relationship on cyclic pentapeptide ET_A antagonists (27). In the course of these extensive modifications, it was also found that certain structural alterations intensified ET_B affinity of some of these analogues. Further modification has resulted in the development of a potent and selective ET_B antagonist, BQ-788 [*N-cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine] (Fig. 1). We herein describe *in vitro* and *in vivo* the biological profile of the compound.

MATERIALS AND METHODS

Materials. Compounds 1–5 (Table 1) were synthesized as a free acid except for compound 5 (BQ-788) using conventional liquid-phase peptide synthesis in our chemistry laboratory. BQ-788 was prepared as a sodium salt by treatment of the corresponding free acid with $NaHCO_3$. All of these compounds were characterized by consistent ^{1}H NMR and high-resolution fast-atom-bombardment mass spectra. BQ-123 as a sodium salt and an ET_B-selective agonist, BQ-3020, were also prepared in house according to the previously described methods (refs. 23 and 28, respectively). ET-1 and ET-3 were purchased from Peptide Institute (Osaka). ^{125}I-ET-1 (2000 Ci/mmol; 1 Ci = 37 GBq) was purchased from Amersham.

Membranes from porcine cerebellum were prepared as described (16). pCASM cells were obtained by the previously described explant method with minor modifications (29). hGH cells and human neuroblastoma cell line SK-N-MC cells were purchased from Dainippon Seiyaku (Osaka). pCASM cells and SK-N-MC cells were cultured in Dulbecco's mod-

Abbreviations: ET, endothelin; ^{125}I-ET-1, ^{125}I-labeled ET-1; pCASM, porcine coronary artery smooth muscle; hGH, human Girardi heart; FCS, fetal calf serum; BSA, bovine serum albumin; $[Ca^{2+}]_i$, intracellular free calcium ion concentration.

*To whom reprint requests should be addressed.

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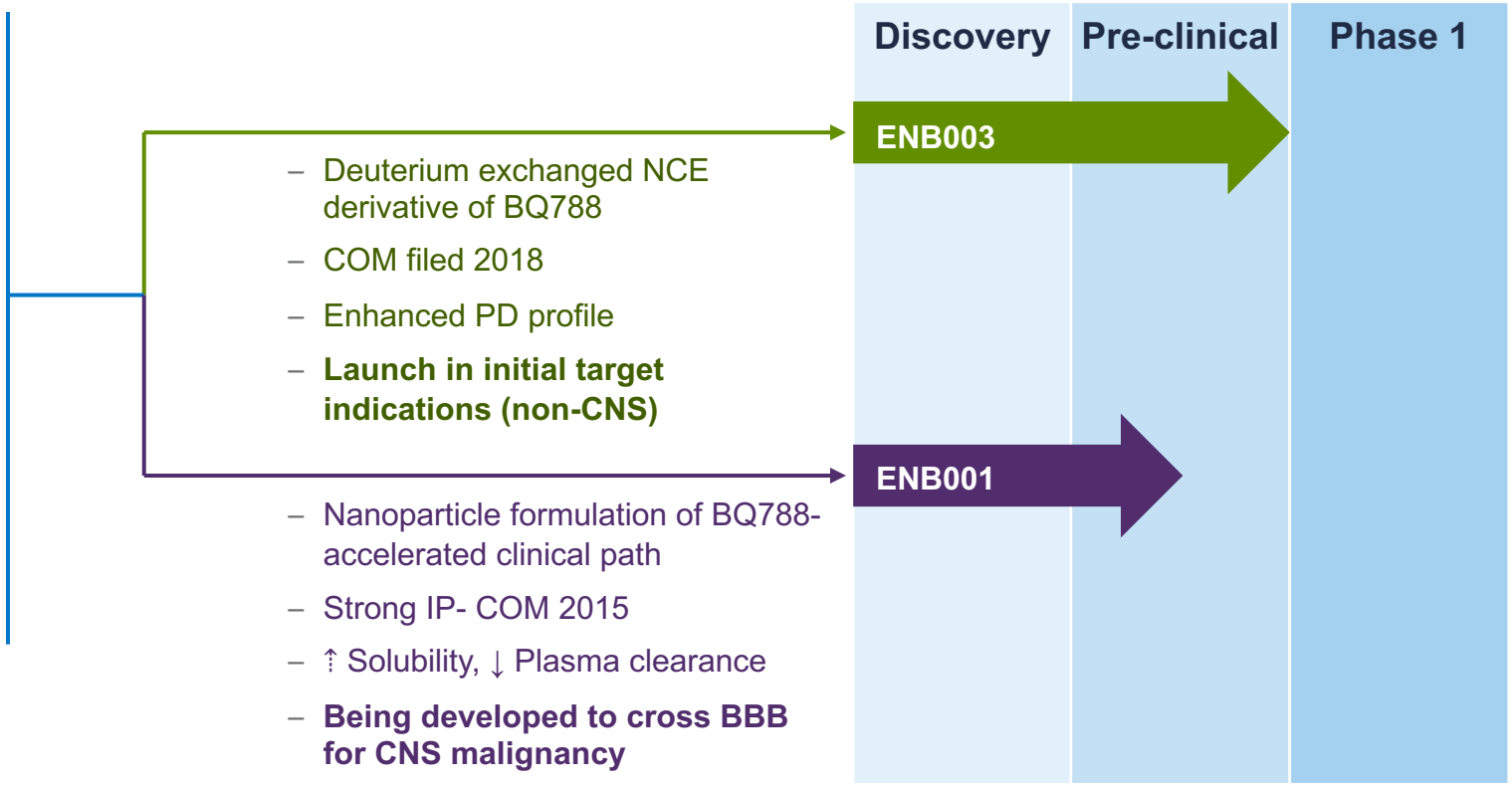
Ishikawa et al, *PNAS* 1994

First-in-class ENB-001 and NCE ENB-003: 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
- **Orphan drug designation for melanoma awarded by FDA to ENB**
- **Low solubility, rapid plasma clearance**

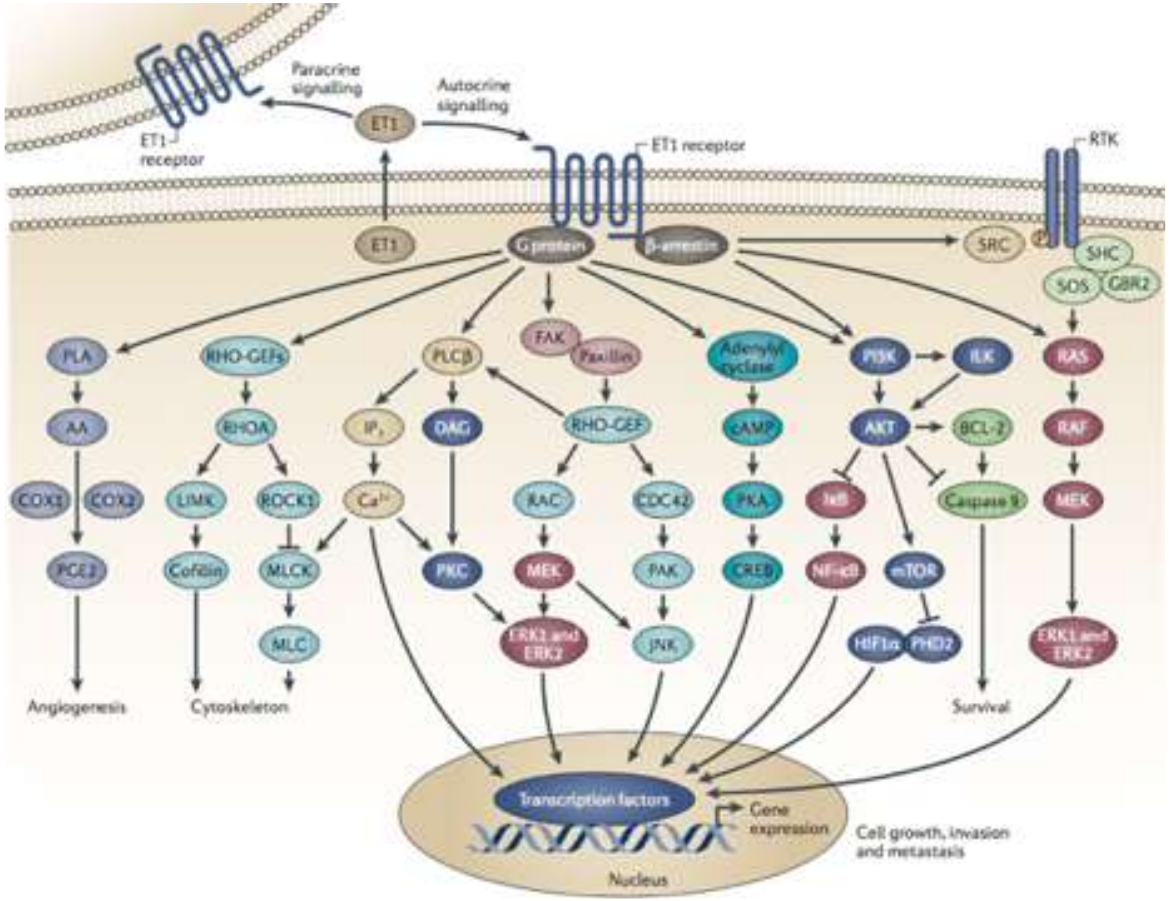


BBB: Blood-brain barrier; **CNS:** Central nervous system; **COM**: composition of matter; **CV:** Cardiovascular; **IP:** intellectual property; **NCE:** new chemical entity; **PD:** Pharmacodynamic

ETBR expression across multiple cancer types

The ETBR is a master regulator of melanoma progression

- ETBR is a melanoma tumor progression marker
  → Expression of ETBR, as well as ETBR-activating ligands ET-1/ET-3, increase during melanoma progression, forming an autocrine loop
- Promotes de-differentiation of melanoma cells
- Suppresses apoptosis by upregulating PARP-3 and BCL-2A1
- Activates intracellular kinases: MEK, RAF, AKT, FAK
- Upregulates key factors that promote melanoma progression: CXCL1, CXCL8, VEGF, MCAM, MMP-2, MMP-9, MTI-MMP, BCL21a, PARP-3, osteopontin, HIF-1 alpha, COX1/COX2, PGE2, GNAQ
- Downregulates factors that suppress melanoma invasion (e.g., E-cadherin)



Source: Rosano et al, *Nature Reviews Cancer* 2013

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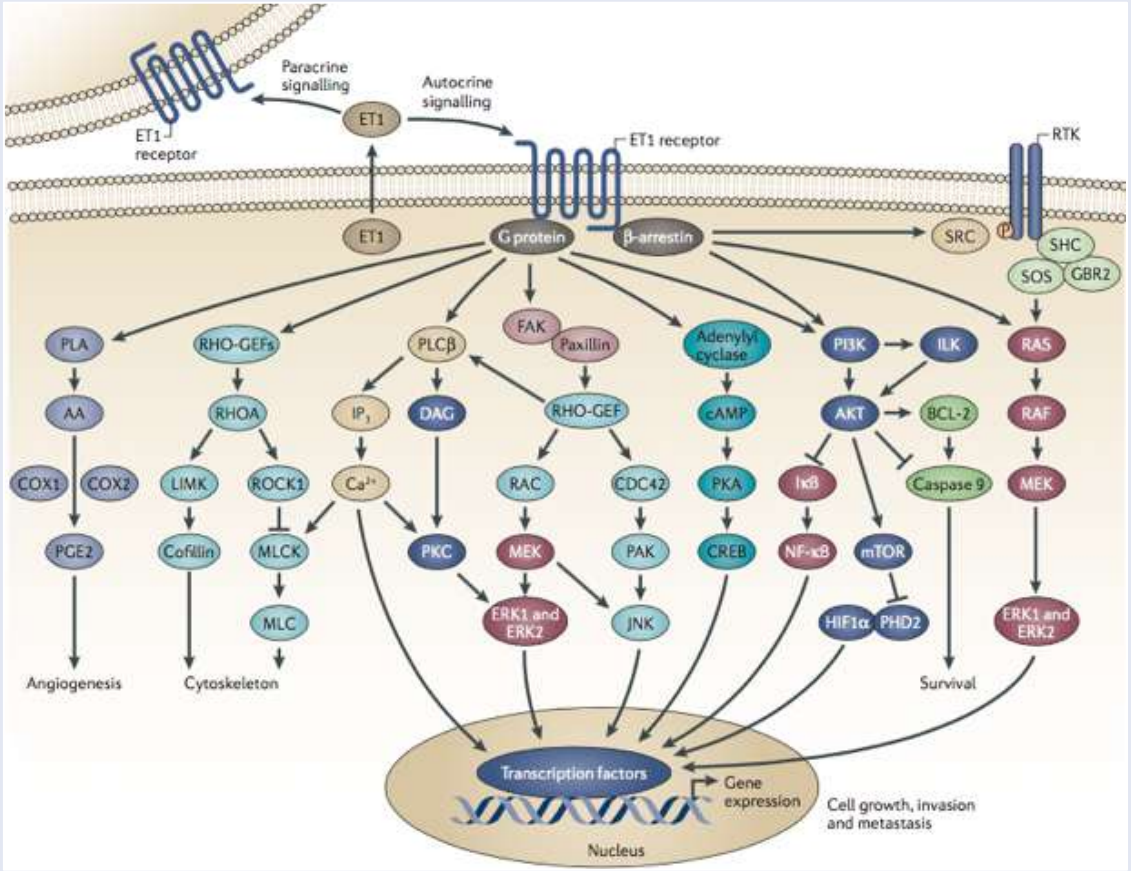


Source: Rosano et al, *Nature Reviews Cancer* 2013

ETBR is highly expressed on TAMs, PSCs and blood vessels in pancreatic cancer

TAMs promote

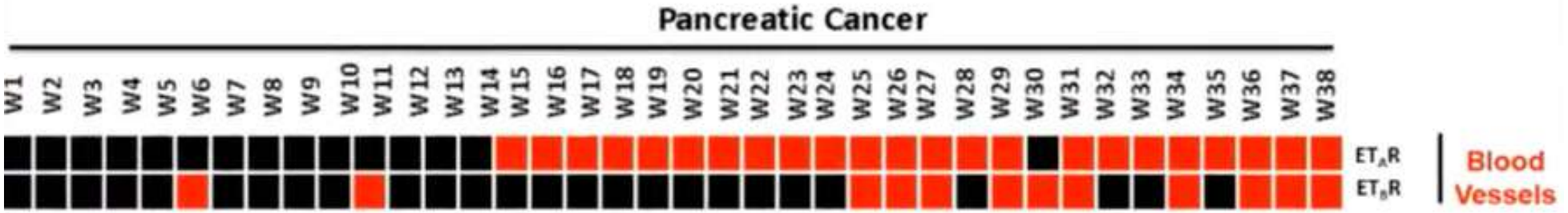
- Immune suppression
- Invasion/metastasis
- Vascular remodeling
- Chemotherapy resistance
- Tumorigenicity
- **BQ788 blocks TAM function**

PSCs block

- IO efficacy and cause desmoplasia, metastasis and chemoresistance
- PSC responsible for IO resistance in preclinical models of pancreatic cancer
- **BQ788 blocks PSC function: and production of ECM and CTGF**

Grid map representation of ET-1, ETAR and ETBR expression in blood vessels

- ETBR expressed on 31.5% of blood vessels in the TME



M. Jain, unpublished data, seminar video: https://youtu.be/e2yt_gJqZzk

CTGF: connective tissue growth factor; **ECM:** extracellular matrix; **ETAR:** endothelin receptor A; **PCS:** pancreatic stellate cell; **TAM:** tumor associated macrophage

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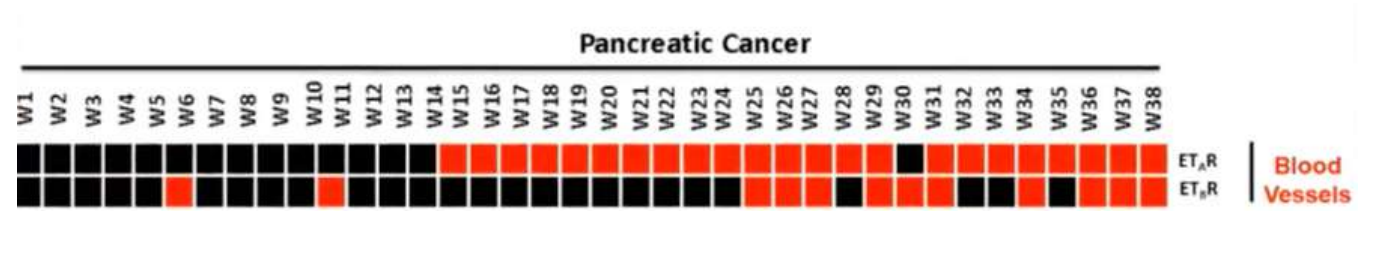

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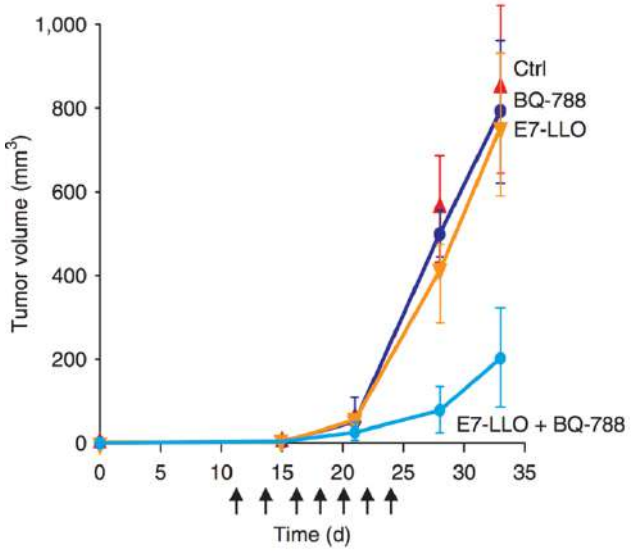
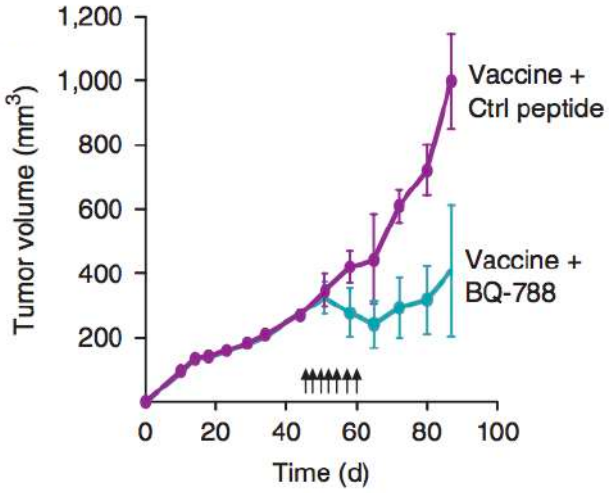
ETBR blockade enhances IO efficacy and prolongs survival in preclinical models of lung and ovarian cancer by recruiting TILs

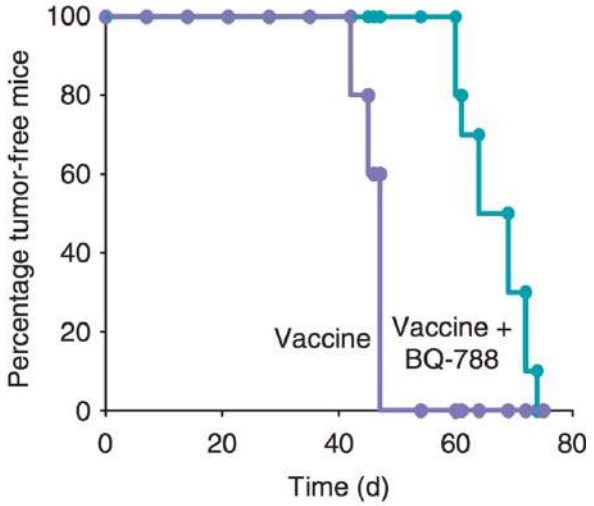
ETBRi stimulates T-cell infiltration and enhances IO efficacy in lung cancer model in mice



ETBRi stimulates T-cell infiltration and enhances IO efficacy in ovarian cancer model in mice



ETBRi prolongs survival in ovarian cancer model in mice

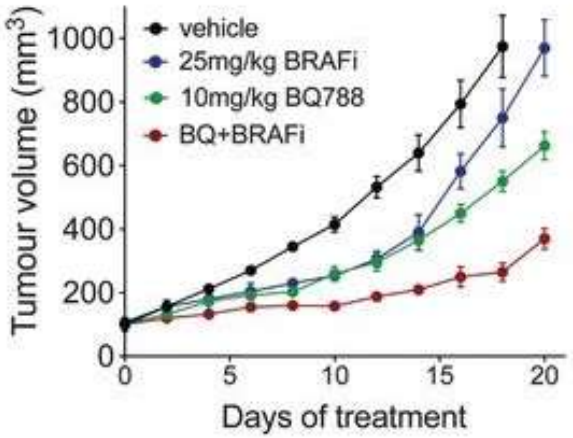


ETBRi: ETBR inhibition

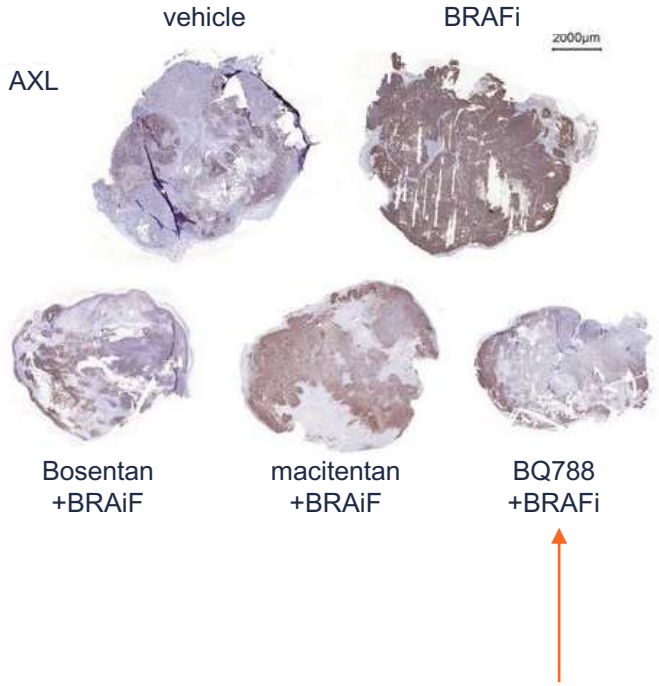
Buckanovich et al, *Nature Medicine* 2008

ETBR blockade overcomes resistance to MAPK pathway inhibitors

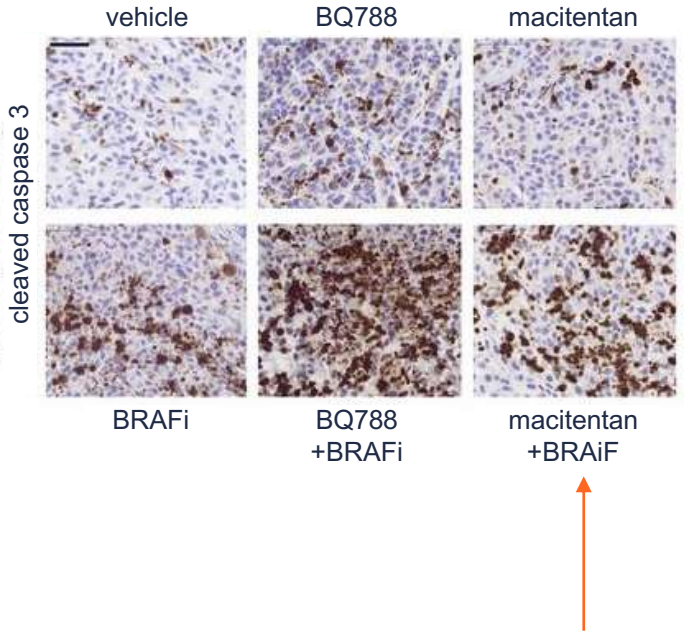
ETBRi suppresses drug resistance to BRAFi



ETBRi prevents outgrowth of drug-resistant cells



ETBRi enhances cell death induced by BRAFi

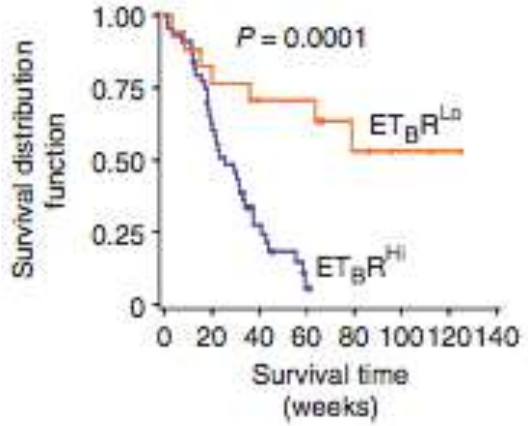


BRAFi: BRAF inhibition

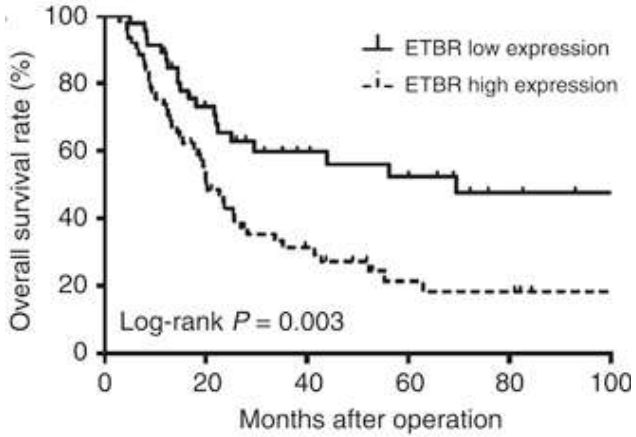
Smith et al, *EMBO Molecular Medicine* 2017

Immune escape due to ETBR overexpression in TME correlates with cold tumors and poor survival across multiple cancer types

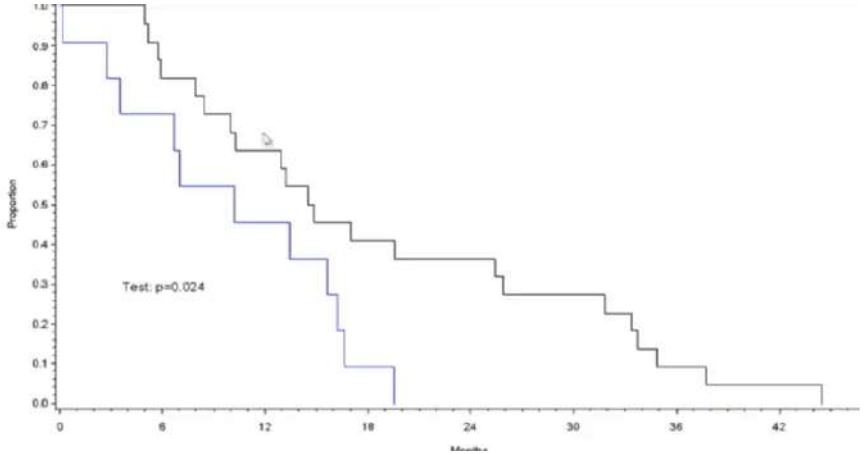
Ovarian cancer
Buckanovich et al, *Nature Medicine* 2008



Squamous cell carcinoma
Tanaka et al, *British Journal of Cancer* 2014



Pancreatic cancer
Jain M, unpublished data, seminar video: https://youtu.Be/e2yt_gjqzzk

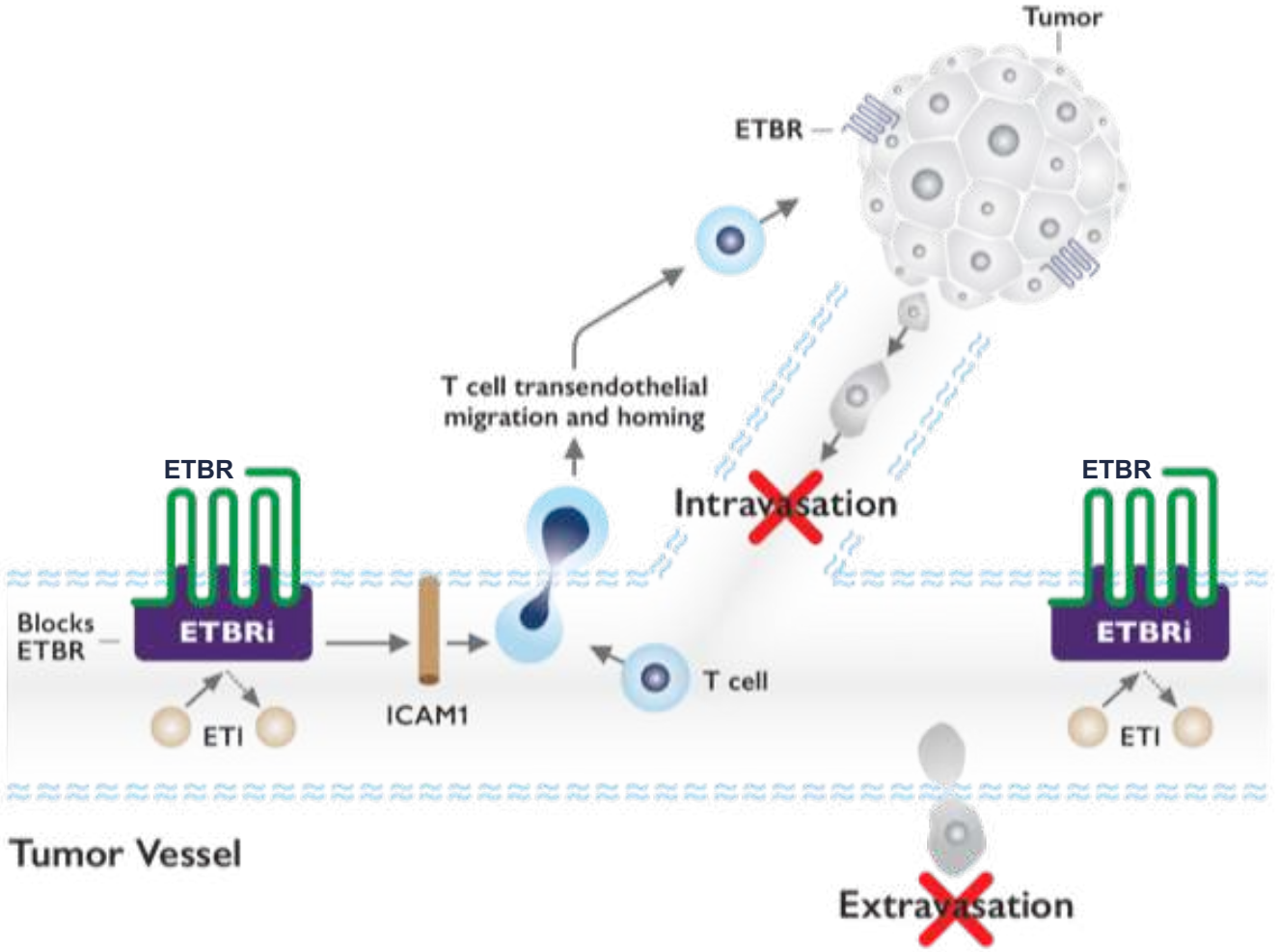


Switching immune-suppressed “cold” TMEs to “hot” TMEs

ETBRi MoA in cancer IO

- Our products 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

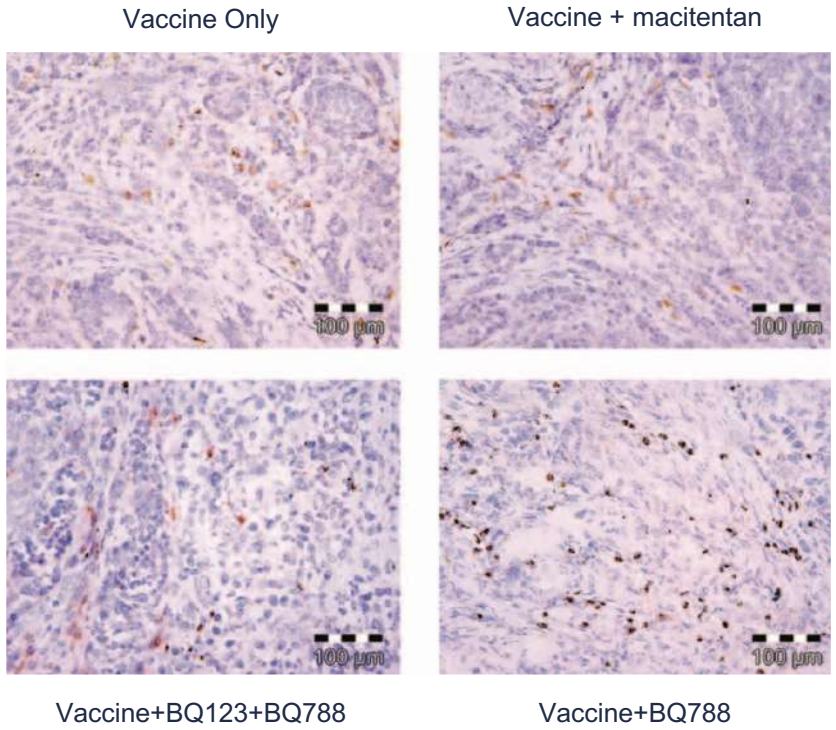
  → Activated T cells are then able to infiltrate the tumor and kill it
- Our products also block ETBR expressed on the tumor cells, preventing metastatic spread

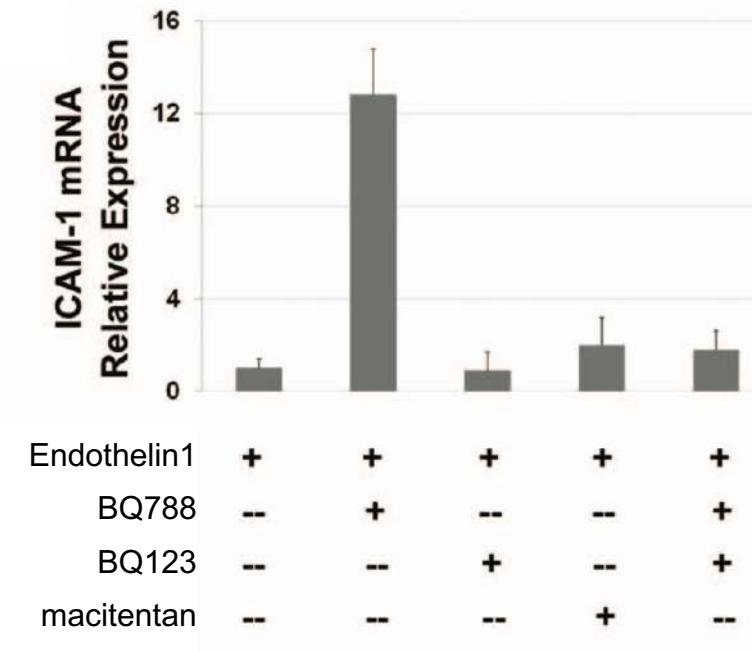


MoA: mechanism of action

ETAR blockade abolishes TIL recruitment by BQ788

- Dual ETAR/ETBR antagonist macitentan fails to recruit CD8+ TILs or upregulate ICAM-1
- Addition of ETAR antagonist BQ123 blocks BQ788 from recruiting TILs and upregulating ICAM-1
- **ALL** previous attempts to target the endothelin axis in clinical trials utilized ETAR blockade





Coffman et al, *Journal of Cancer Biology & Therapeutics* 2013

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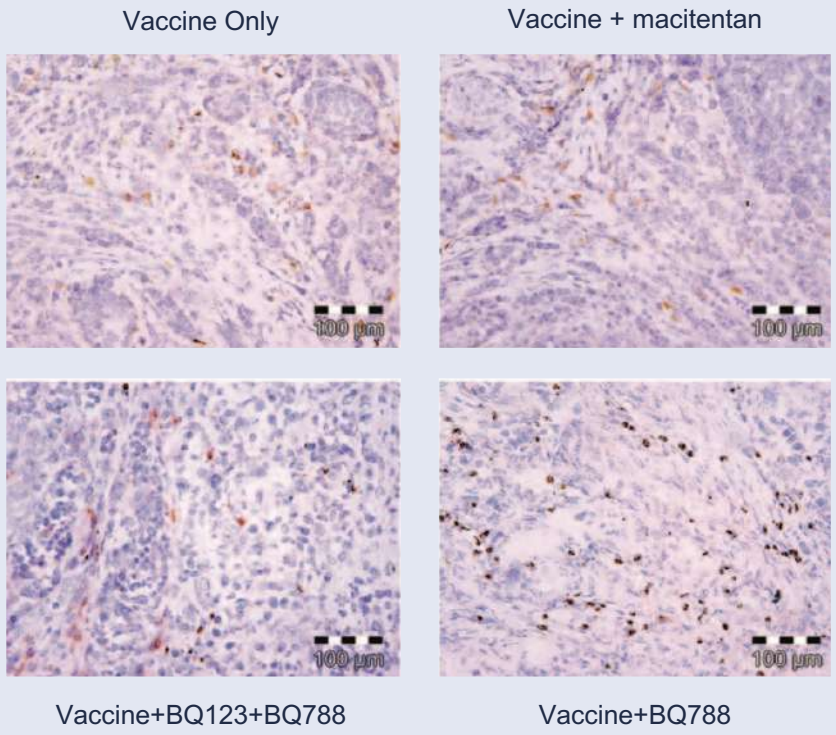
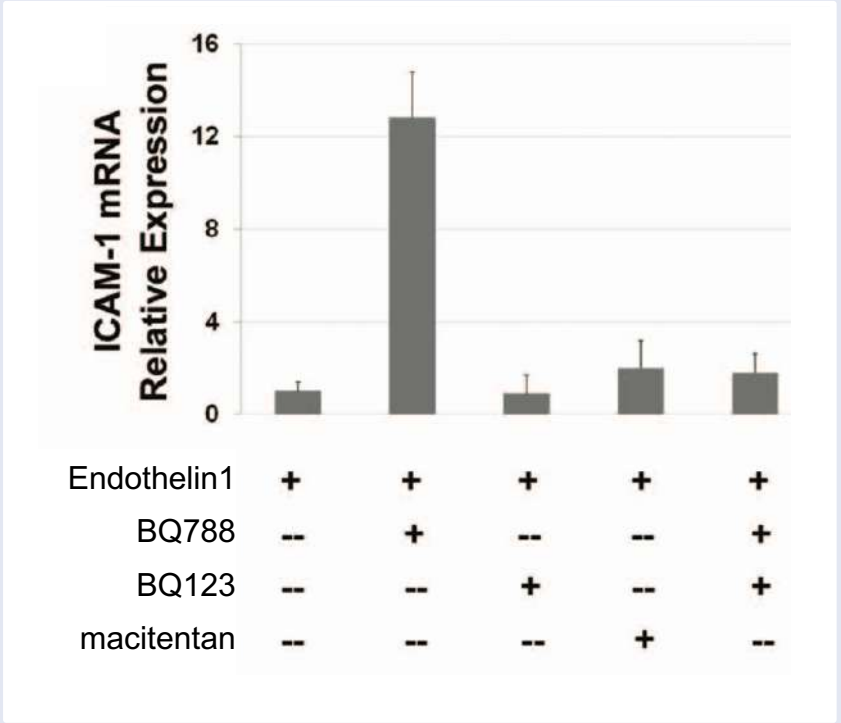


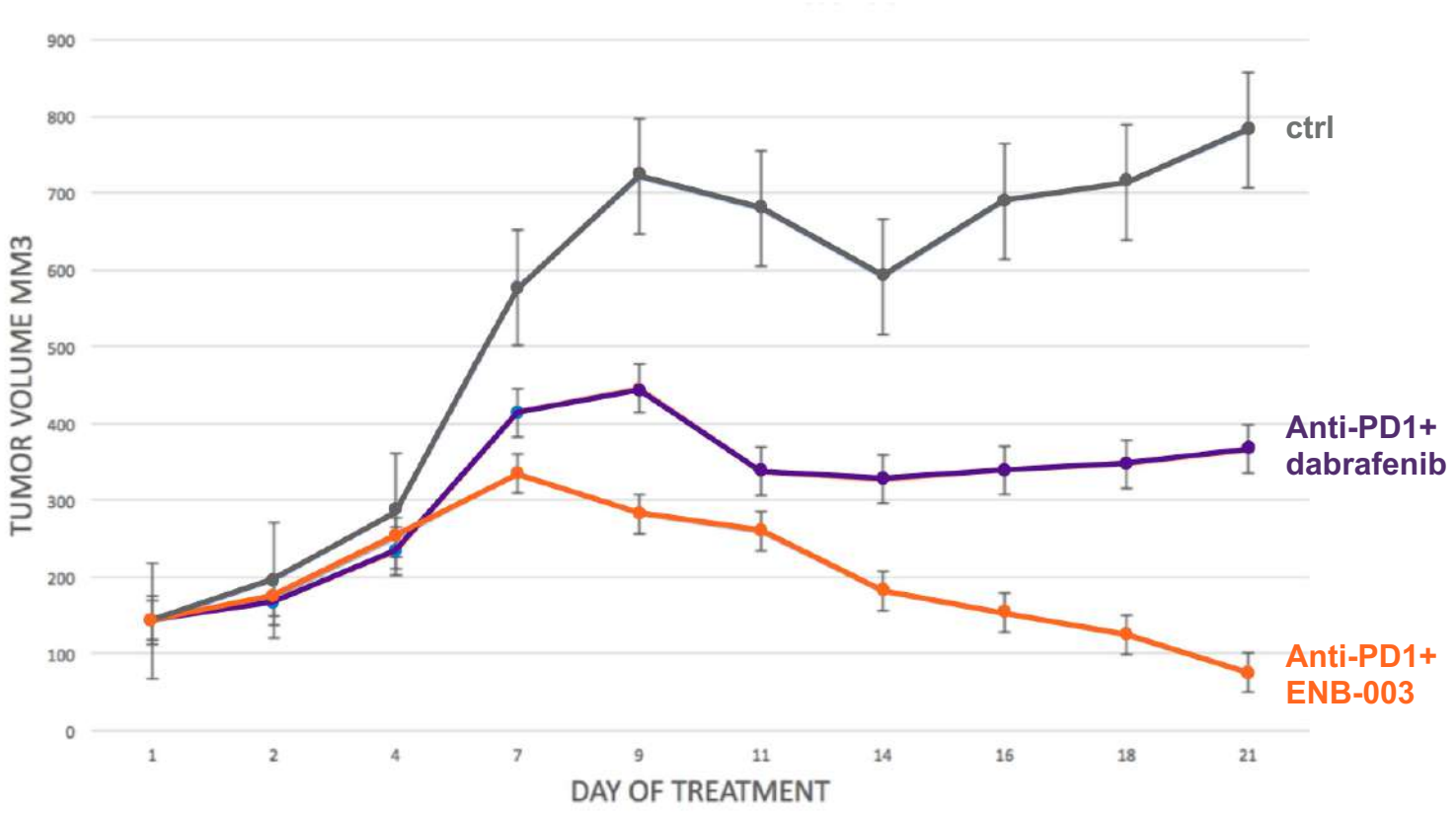


Coffman et al, *Journal of Cancer Biology & Therapeutics* 2013

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 (slide 17)*
- Previously tested SoC drug combinations using this model failed to shrink tumors and all resulted in eventual drug resistance (see next slide)



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 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

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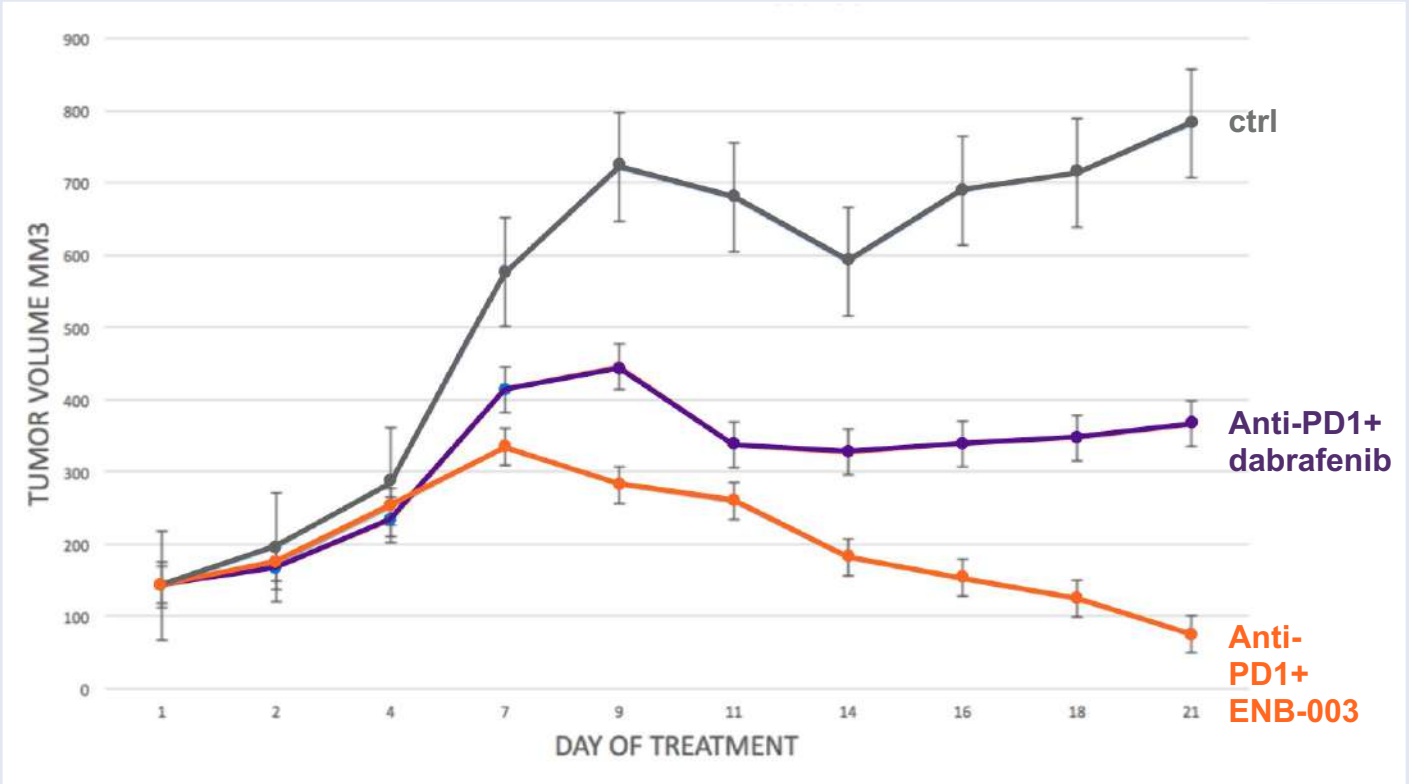


Source: internal study, unpublished

ENB-003 + anti-PD1 combination show superior response to previous anti-PD1 combination studies with SM1 melanoma cell lines

- Published studies demonstrate lack of efficacy of anti-PD1 as a single agent in the SM1 cell line
- Treatment initiated when tumor sizes were much smaller than in our study (14-65 mm3 vs 150 mm3)
- Resistance emerged in all trial arms by day 25 post-tumor inoculation with no tumor elimination noted in any arms with any combination

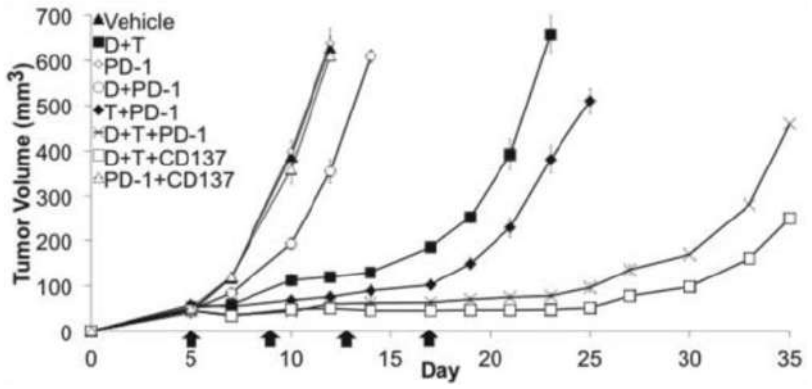
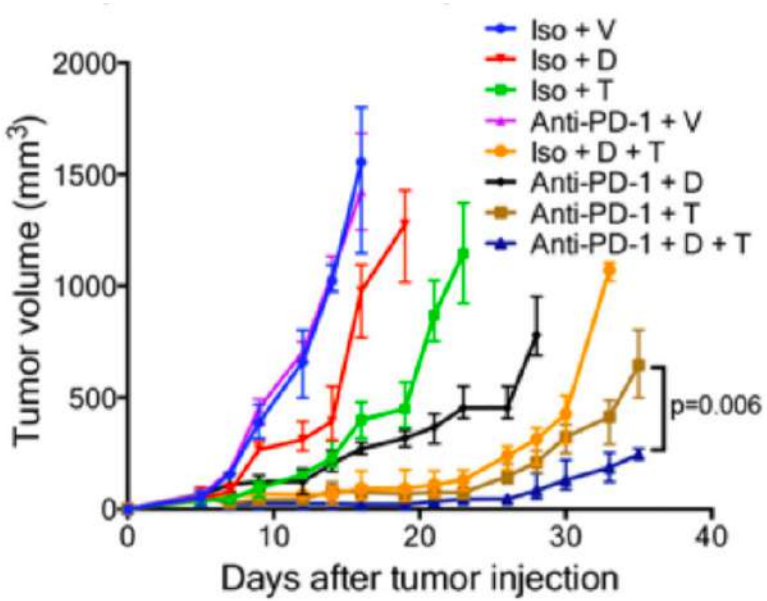


Figure 1. Enhanced *in vivo* antitumor activity with dabrafenib (D) + trametinib (T) combined with PD-1 checkpoint blockade against SM1 tumors. *In vivo* tumor growth curves. SM1 bearing C57BL/6 mice were treated when tumors were 3–5 mm with D 30 mg/kg and T 0.15 mg/kg combination via oral gavage daily, 4 doses of 200 μg of anti-PD-1 (PD-1), D + PD-1, T + PD-1, D + T + PD-1, D + T + anti-CD137 (CD137), PD-1 + CD137 or vehicle + isotype control Ab (4 mice in each group). This is representative graph of a three times repetition of this experiment.

Homet Moreno et al, *Oncoimmunology* 2015



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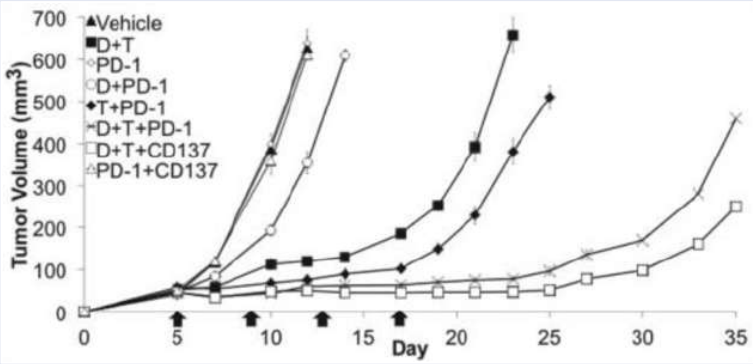

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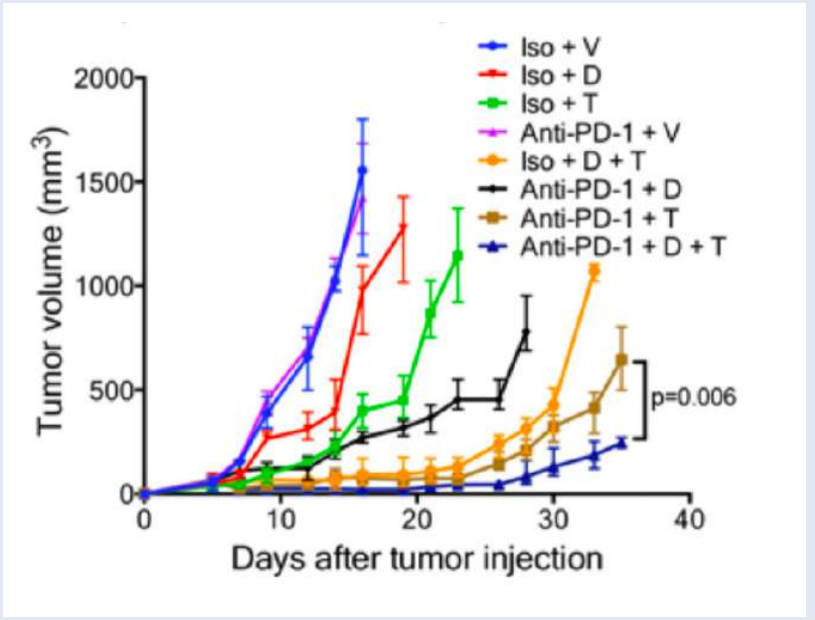


Hu-Lieskovan et al, *Science Translational Medicine* 2015

Creating intratumoral TLOs

TLO formation is associated with favorable clinical prognosis and response to IO therapy

"…within the tumor microenvironment of TLSs, whose presence has a positive impact on tumor prognosis. TLSs are transient ectopic lymphoid aggregates displaying the same organization and functionality as canonical secondary lymphoid organs, with T-cell-rich and B-cell-rich areas that are sites for the differentiation of effector and memory T cells and B cells"

– Germain et al, *Frontiers in Immunology* 2015

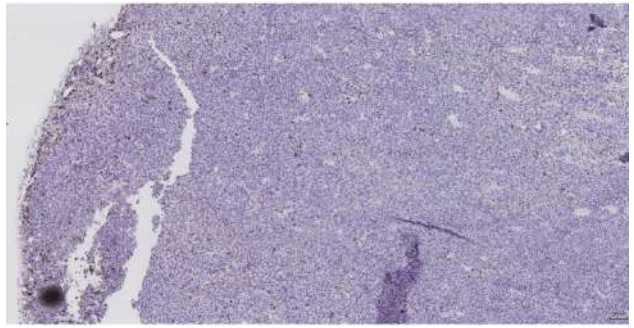
"TLSs present in human solid tumors are essential for the shaping of a favorable immune micro-environment to control tumor development in most cases. They represent a formidable school for T-cell priming, B cell activation, and differentiation into plasma cells and an exquisitely located factory for antibody production. The manipulation of TLS neogenesis and maintenance represents, therefore, an exciting task to set up efficient anti-cancer vaccine strategies leading to long lasting anti-tumor adaptive responses."

– Teillaud et al, *Frontiers in Immunology* 2017

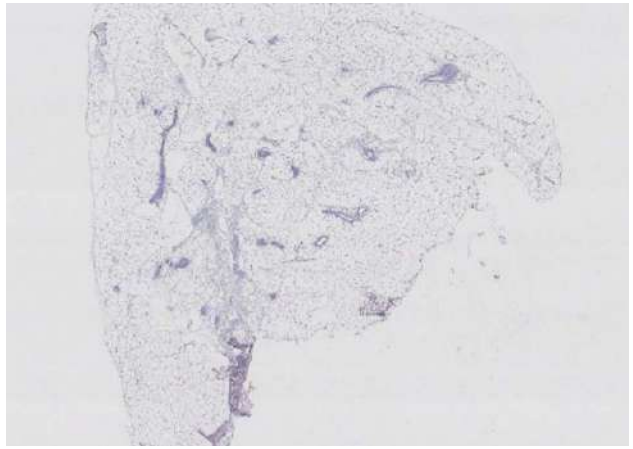
TLS: Tertiary lymphoid structure

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

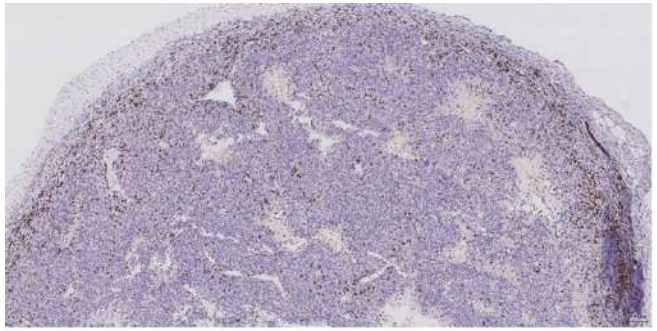


anti-PD1+ENB-003- No residual tumor

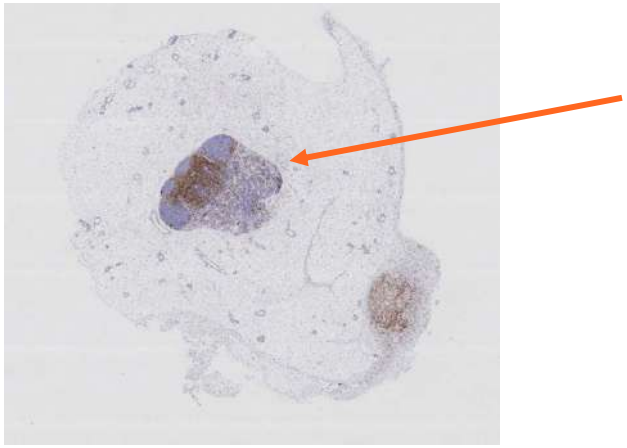


*brown stain

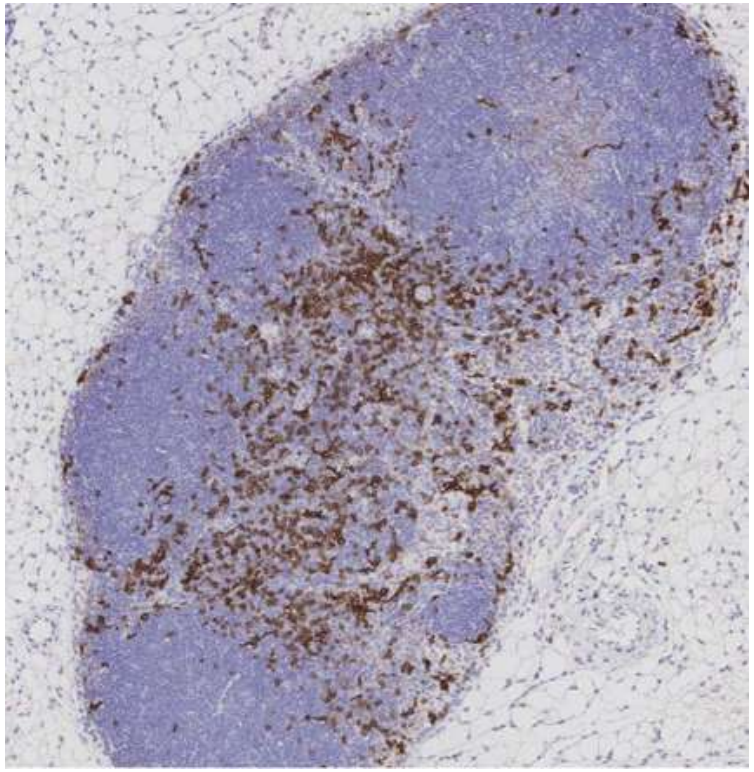
Anti-PD1+ dabrafenib: Increase in TILs, predominantly peripheral distribution



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

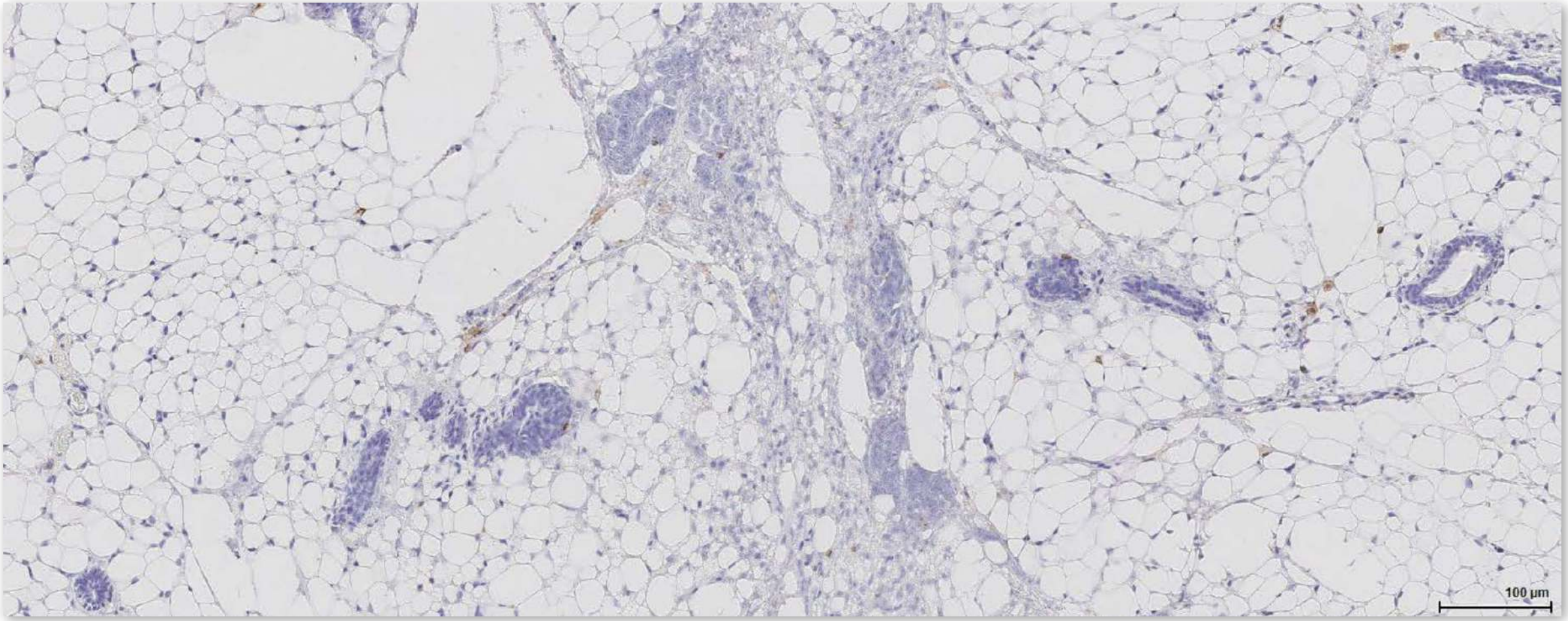


TLO (Hi mag)

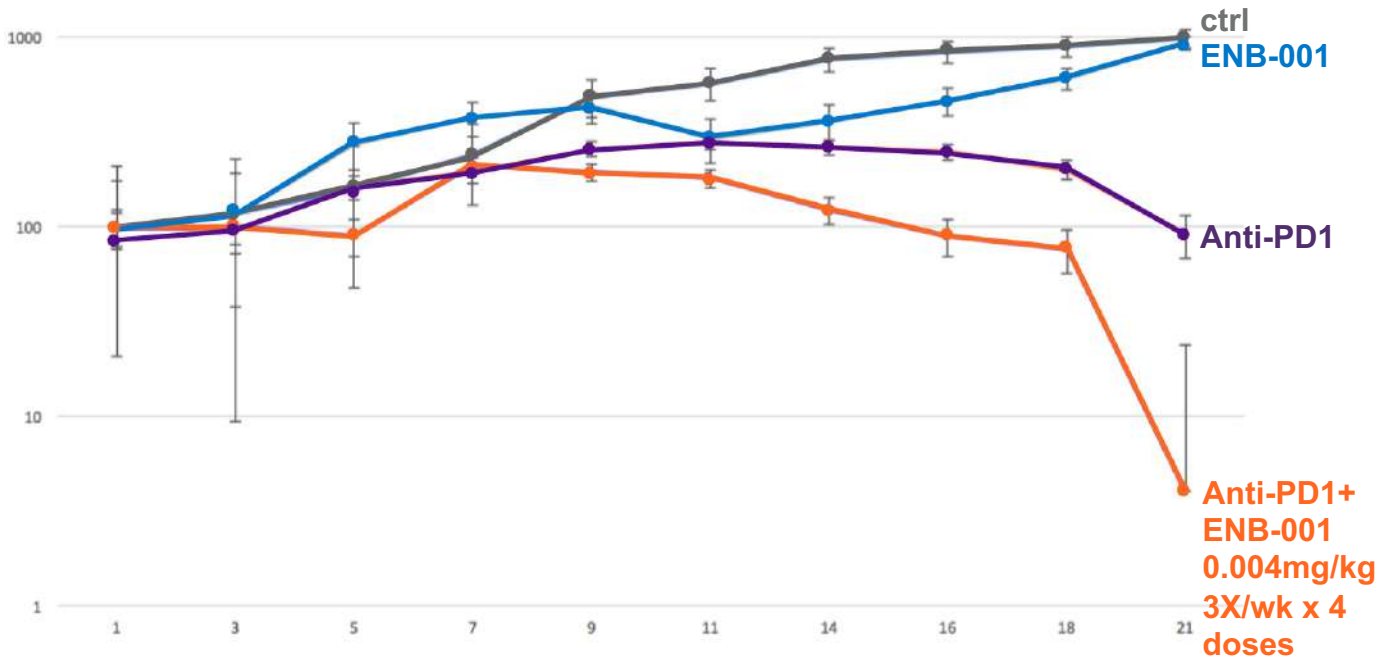


** TLOs are functionally equivalent to lymph nodes, produce tumor-specific T- and B-cells: **"antibody factories to fight cancer,"** induce long lasting anti-tumor immunity and are associated with favorable clinical prognosis in multiple cancers

High magnification reveals mature adipocytes, with no tumor cells evident in ENB-003- + anti-PD1-treated melanoma tumor

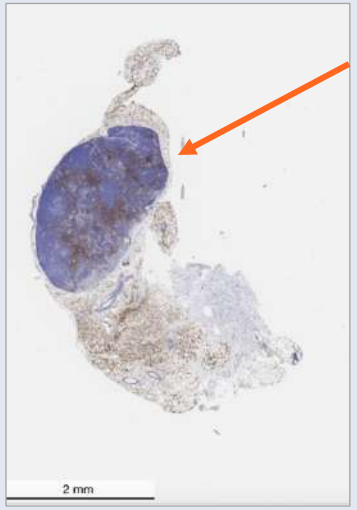


ENB-001 + anti-PD1 combination reproduces tumor eradication and TLO formation observed with ENB-003 in SM1 model

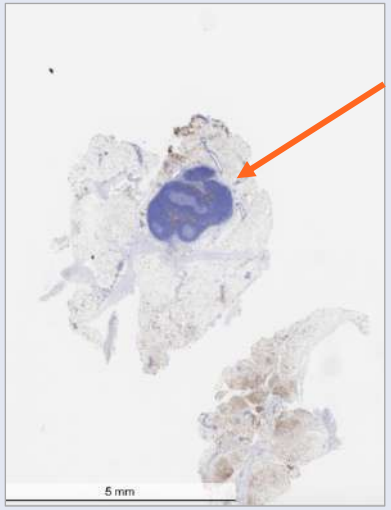


Source: Internal study, unpublished

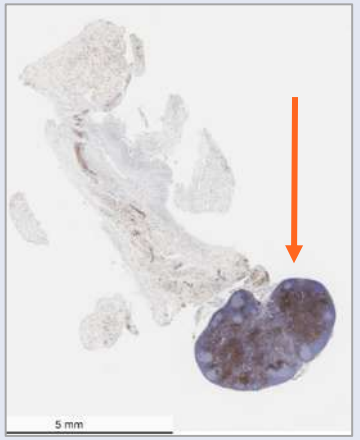
TLO formation observed with broad dosing range of ENB-001 and ENB-003



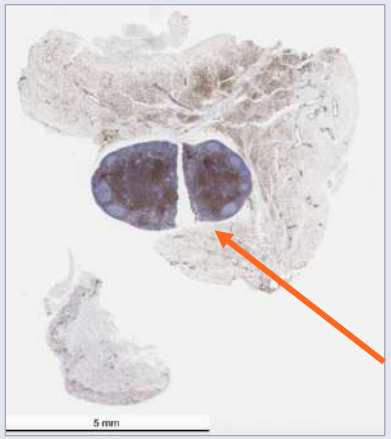
ENB-003 Dose 1



ENB-003 Dose 2

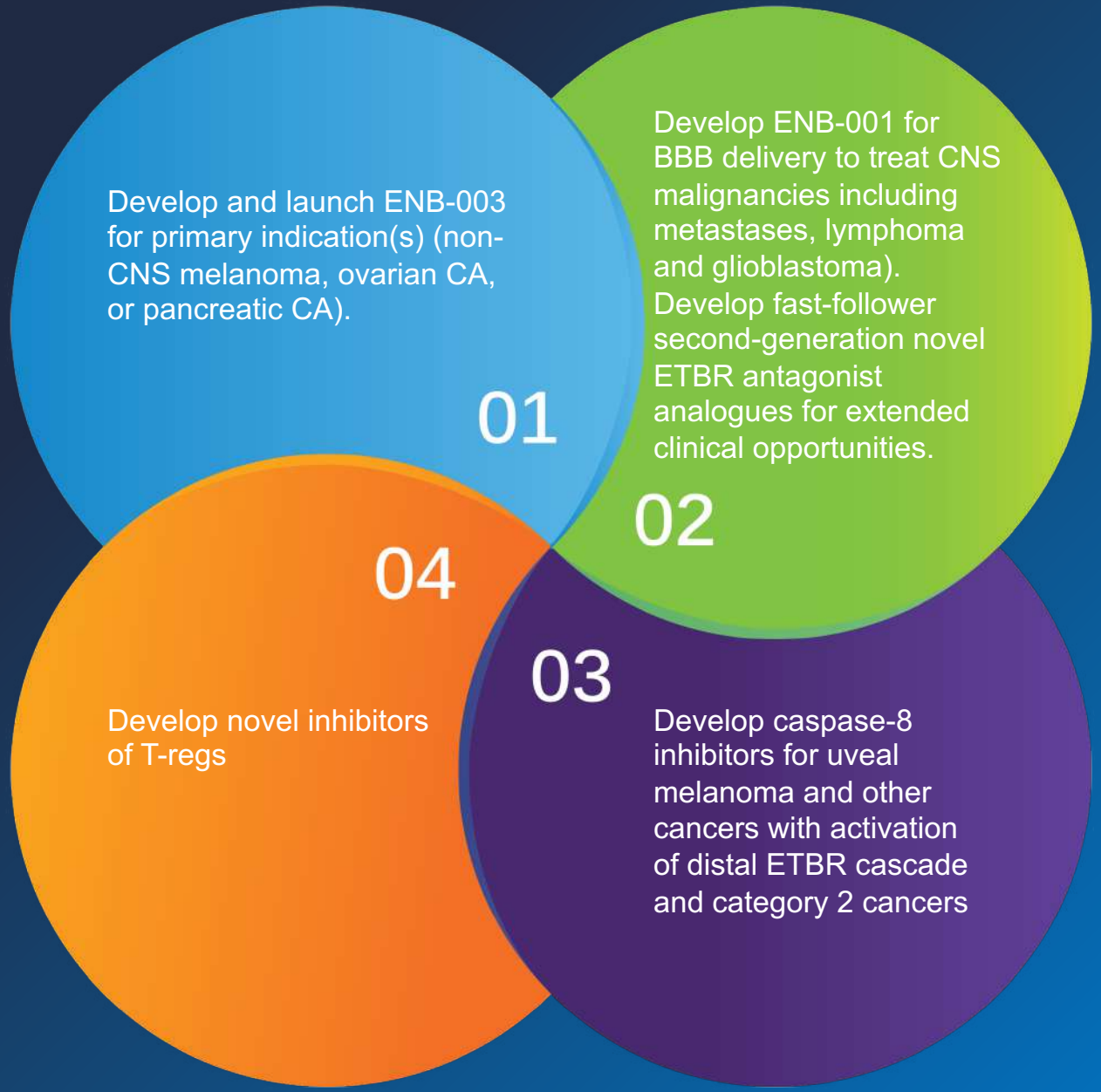


ENB-001 Dose 1



ENB-001 Dose 2

Business model



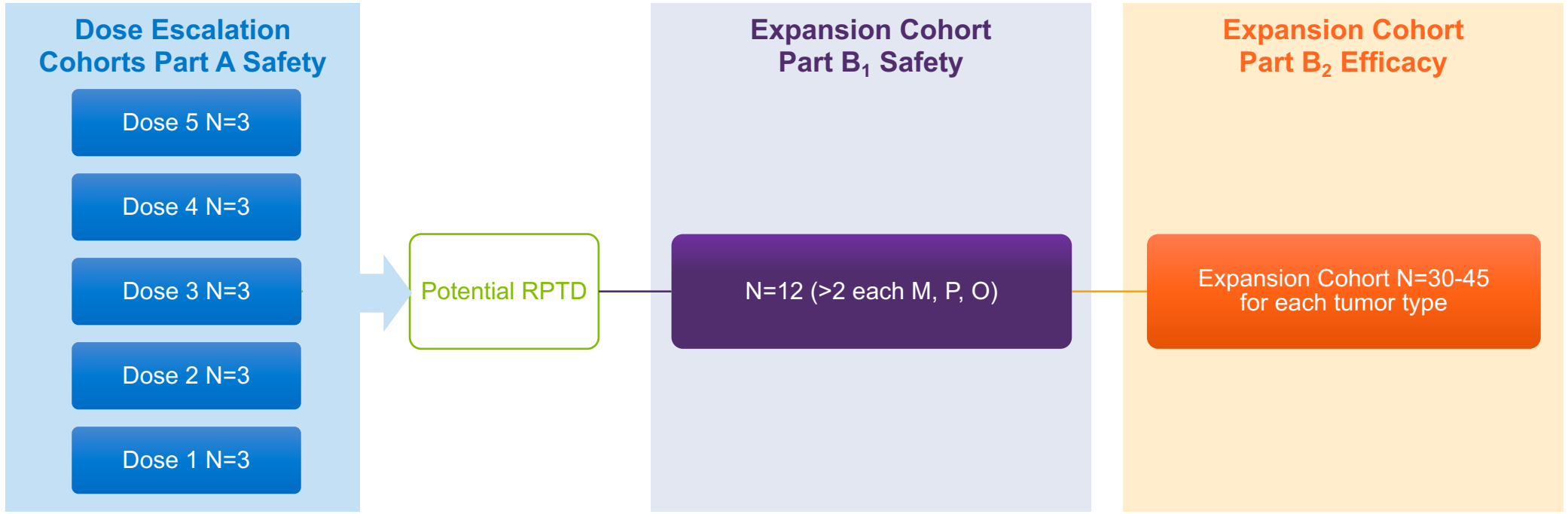
A platform for sequenced immuno-oncology growth opportunities

CATEGORY 1 CANCER ETBR+ CANCER CELL, ETBR+TME	**CATEGORY 2 CANCER** ETAR+ CANCER CELL, ETBR+TME
Melanoma*	Ovarian*
Gliboblastoma	Nasopharyngeal
Astrocytoma	Colon CA
Pancreatic CA*	Breast CAA
Small cell lung	Renal CA
Esophageal CA	Thyroid CA
Bladder CA	Gastric CA
Vulvar CA	CNS Lymphoma (ETBR+ TME)
ENB-001 inhibits metastasis and recruits TILs	ENB-001 recruits TILs (Addition of caspase-8 inhibitor to block metastasis downstream of ETAR without causing immunosuppression)

CA: Cancer

*First anticipated indications

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

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	Provisional COM patent filed 2018	Formulation COM filed 2016-Nanoparticle formulation supports COM similar to NCE due to strict FDA guidelines regarding bioequivalence
Method of use	Combination with anti-PD1 and other IO therapies for the treatment of cancer	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	Application for melanoma in preparation	Awarded by FDA for melanoma in 2016: provides 7-year market exclusivity post FDA approval

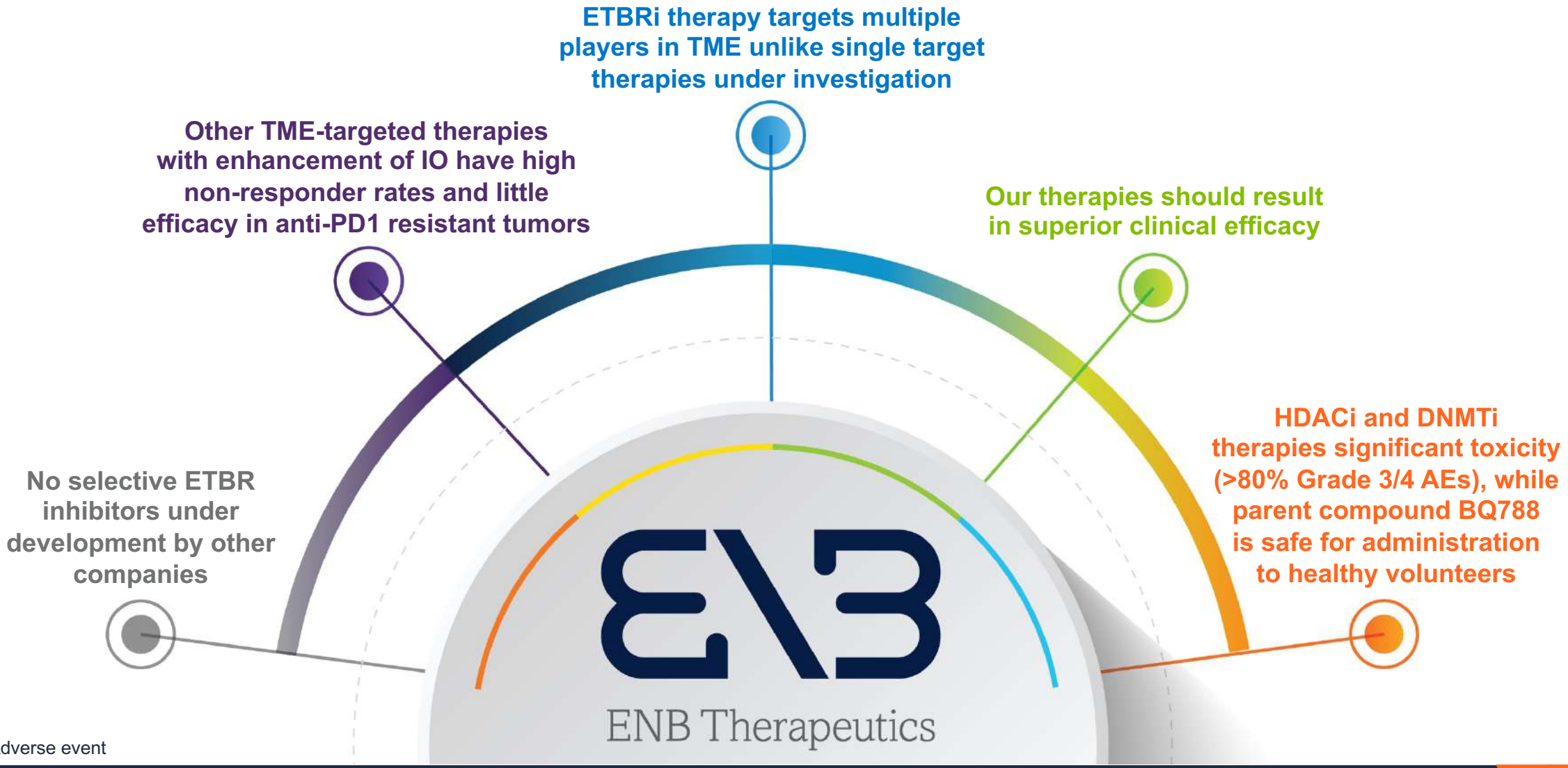
IHC: Immunohistochemistry

Competitive landscape

Drug Class		ETBRi	VEGFi	IDOi	CXCR4i	Adenosine Ri	HDACi	DNMTi
Drug name(s)		**ENB-001, ENB-003**	Bevacizumb	Epacadostat	BL08040	CPI-444,	Romidepsin, Vorinostat	Vidaza
TME Target	ETBR	✓						
	VEGF	✓	✓					
	DCs	✓		✓				
	TAMs	✓		✓				
	TANs	✓						
	CAFs	✓			✓			
	EC	✓			✓			✓
TME effect	**TLO formation**	✓						
	Reverse anti-PD1 resistance	✓						
	Vasculogenic mimicry	✓						
	Anti-angiogenic	✓	✓					
	TIL recruitment	✓	✓		✓		✓	
	Enhances T-cell survival	✓		✓		✓		
	Enhance tumor immunogenicity							✓

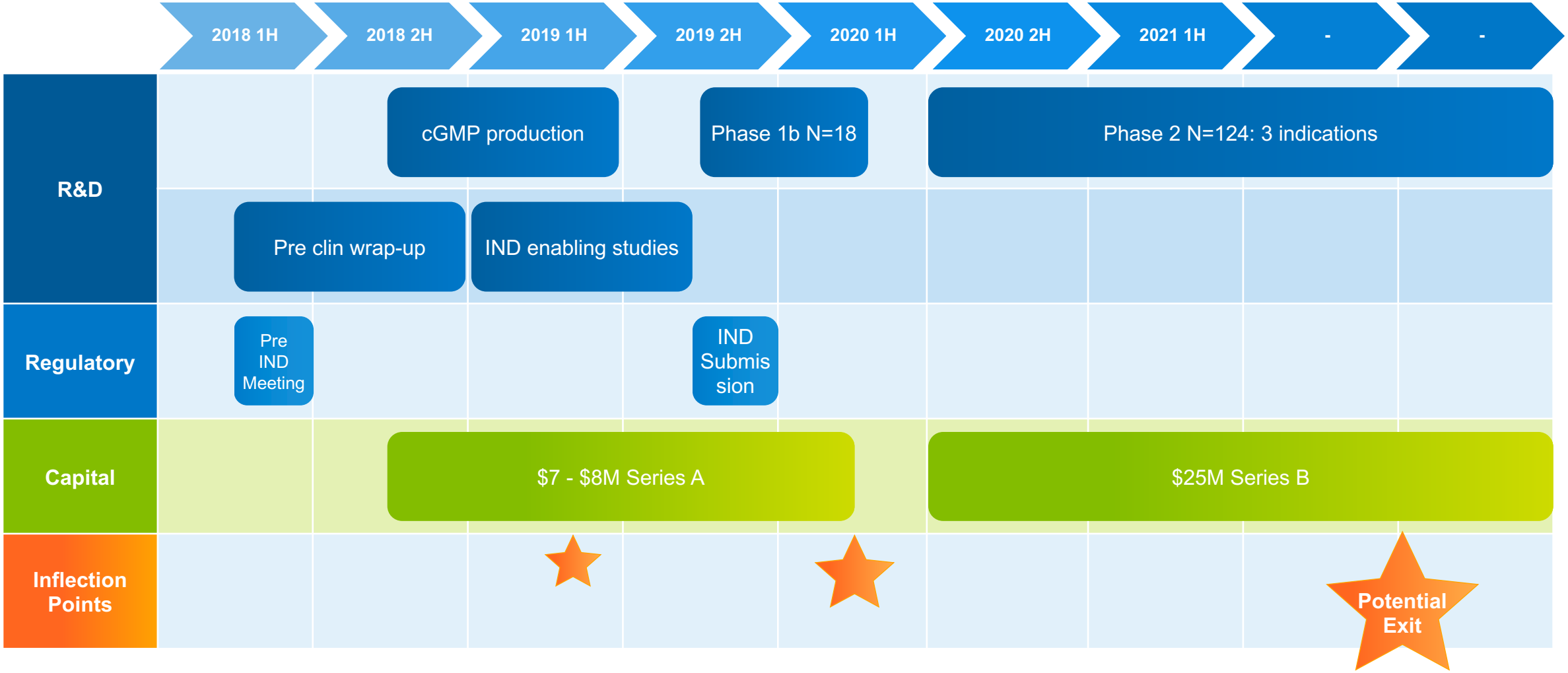
CAF: cancer-associated fibroblast; **DNMTi:** DNA methyltransferase inhibitor; **HDACi:** Histone deacetylase inhibitor; **IDOi:** Indoleamine inhibitor; **TAN:** tumor-associated neutrophil; **VEGFi:** vascular endothelial growth factor inhibitor

ENB's Advantage



AE: Adverse event

Milestones: Clinical development ENB-003



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

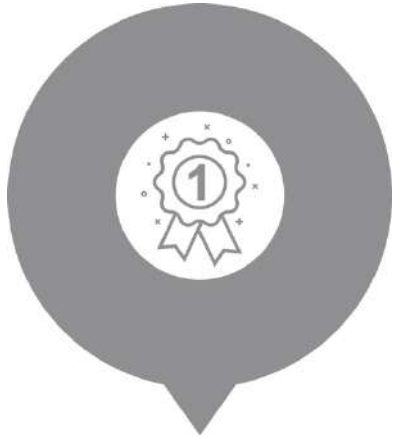
NEW YORK STATE OF OPPORTUNITY. | New York Ventures

pipeline ANGELS

ALEXANDRIA VENTURE INVESTMENTS

NY

Blazing a trail that benefits patients and investors



Potential First and Best-in-Class
Selective Endothelin B Receptor (ETBR) Inhibitors to reverse immunotherapy resistance

- Company founded to exploit the recent discovery that selective B receptor blockade is required for efficacy- all previous attempts to block endothelin axis failed due to non-selective A/B blockade
- Well understood MOA
- Robust preclinical efficacy across multiple cancers with tumor eradication
- Favorable clinical safety profile of parent compound
- Lead molecule, NCE ENB-003 ready for IND enabling studies
- Potentially synergistic with multiple immunotherapy platforms
- Block resistance to MAPK pathway inhibitors
- ENB-001 in development to deliver compounds across the BBB
- Only class of therapeutic known to induce intratumoral Tertiary Lymphoid Organ (TLO) formation for long term anti-cancer immunity

Blazing a trail that benefits patients and investors

Potential First and Best-in-Class
Selective Endothelin B Receptor (ETBR) Inhibitors to reverse immunotherapy resistance

Strong and Broad IP and Regulatory Exclusivity

Soon-to-be Announced collaboration
with big Pharma partner

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

Short-Term Milestones
IND filing 2Q 2019; PI/PII initiation 3Q 2019

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

Thank You

Contact: sjamal@enbpharma.com