HITLAB

ENB Therapeutics

ENB Therapeutics: Clinical and Scientific Evaluation of ENB-003 for Drug-Resistant Cancers

A Summary of Evidence Paper

This report presents HITLAB's independent evaluation of ENB Therapeutics, a group-developing therapies to treat drug-resistant cancers

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Executive Summary

Cancer drug resistance remains one of the most significant unmet needs in modern oncology. The World Health Organization reported approximately 20 million new cancer cases and 9.7 million deaths globally in 2022, a burden that continues to accelerate with population growth and aging. **Despite revolutionary advances in immuno-oncology, more than 75% of all cancer patients fail anti-PD-1/PD-L1 immunotherapy.** For microsatellite stable (MSS) tumors, including most ovarian, pancreatic, and many other cancers, immunotherapy is not even approved, leaving patients with few or no viable options after standard-of-care failure.

Endothelin B receptor (ETBR) expression is the best-identified predictor of non-response to anti-PD1 drugs. This suggests a key role of the ETBR in anti-PD1 resistance and highlights the importance of ETBR blockade in overcoming resistance. ENB Therapeutics is a clinical-stage oncology company developing ENB-003, the world's first selective endothelin B receptor (ETBR) inhibitor to reach clinical trials in cancer. ENB-003 overcomes anti-PD1 resistance and restores immune cell access to otherwise immunologically 'cold' tumors. ENB-003 overcomes immunotherapy resistance by acting throughout the tumor microenvironment, restoring T-cell and B-cell infiltration, inducing tertiary lymphoid organ (TLO) formation, and blocking ETBR-driven metastasis. It is a small-molecule suitable for subcutaneous or intravenous administration.

Clinical findings to date are highly promising**: a completed Phase 1 study** with no dose-limiting toxicities across 46 patients; **a 40% objective response rate (ORR) and 80% disease control rate (DCR) in microsatellite stable, platinum refractory/ resistant ovarian cancer patients not expected to respond to immunotherapy**; and durable responses including a 20-month progression-free survival in a sixth-line patient. The therapy is supported by **issued composition of matter and method of use patents through 2039, pharma collaborations with Merck and Coherus, and institutional backing from the MD Anderson Cancer Focus Fund and the Cancer Research Institute.**

This expanded evidence summary draws on peer-reviewed literature to contextualise ENB-003's clinical significance within the global landscape of unmet need. HITLAB has evaluated the available clinical, scientific, and patient-centric evidence and concludes that ENB-003 represents an emerging and highly promising direction in oncology innovation, one that addresses a fundamental and so-far unsolved barrier to effective cancer immunotherapy.

Key Clinical Reality:

- More than 50% of patients do not respond to immunotherapy
- Existing checkpoint inhibitor combinations show limited efficacy in cold tumors
- TME modulators are limited by toxicity and lack of selectivity
- Cell therapies face cost and scalability barriers
- **ETBR-expression is the best-known predictor of resistance to anti-PD1 immunotherapy**
- **ENB-003 is the first selective ETBR inhibitor to overcome anti-PD1 resistance in Phase 1**

Section 1: Global Cancer Burden — Epidemiology and Prevalence

1.1 The Scope of the Cancer Crisis

Cancer remains one of the most significant challenges in global public health, with a substantial and growing disease burden worldwide. According to Globocan 2022 estimates, approximately 20 million new cancer cases and 9.7 million cancer-related deaths occurred globally in 2022. This burden is projected to rise markedly, with annual incidence expected to exceed 35 million cases by 2050. This increase is driven primarily by population growth, aging populations, and the expanding prevalence of key risk factors, including obesity, tobacco use, and physical inactivity (Bray et al., 2024; WHO, 2024; Siegel et al., 2025).

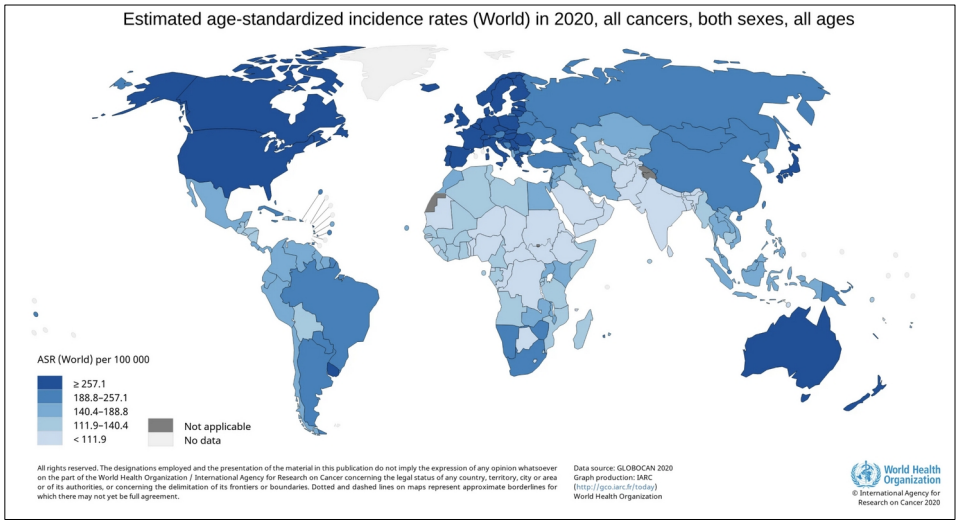


Figure 1.1: Global cancer incidence overview (GLOBOCAN 2022)

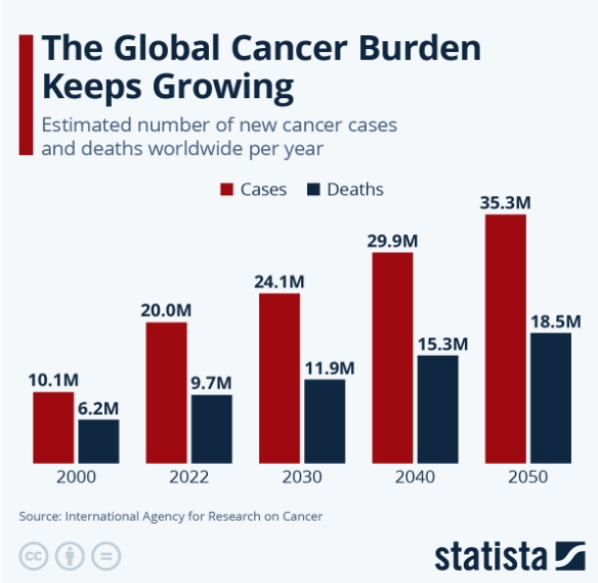


Figure 1.2: Estimated Global Cancer Cases and Deaths (Statista)

1.2 Ovarian Cancer: Epidemiology and Unmet Need

Ovarian cancer remains the most lethal gynecologic malignancy, largely due to late-stage diagnosis and limited treatment options for advanced disease. In the United States, an estimated 20,890 new cases and 12,730 deaths are projected for 2025. Globally, ovarian cancer continues to pose a substantial public health burden, with approximately 313,959 new cases and 207,252 deaths reported in GLOBOCAN 2022 (SEER, 2025; IARC, 2024). Although ovarian cancer accounts for a relatively small proportion of all cancer diagnoses, it remains a leading cause of cancer-related mortality among women because of its high fatality rate and often asymptomatic presentation during the early stages. The disease is influenced by a combination of genetic, reproductive, hormonal, and environmental factors. While most cases occur sporadically, approximately 10–15% are associated with inherited genetic predisposition. In particular, pathogenic variants in the *BRCA1* and *BRCA2* genes are among the most significant hereditary risk factors, conferring lifetime ovarian cancer risks of approximately 44% and 17%, respectively (Wenstrup et al., 2025; Reid et al., 2017; Alsop et al.; Memorial Sloan Kettering Cancer Center; Duan et al., 2023; Tsaousis et al., 2022; Nandini Devi et al., 2024).

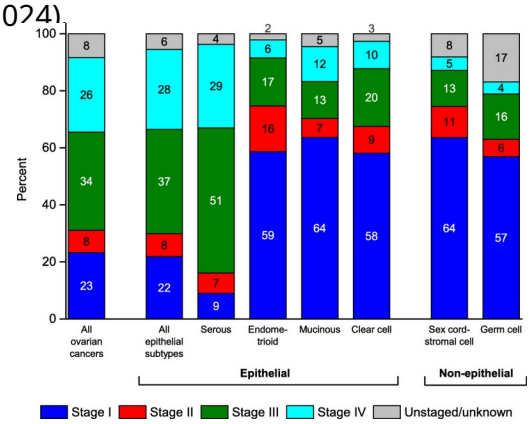


Figure 1.3: Ovarian cancer stage distribution (Torre et al., 2018)

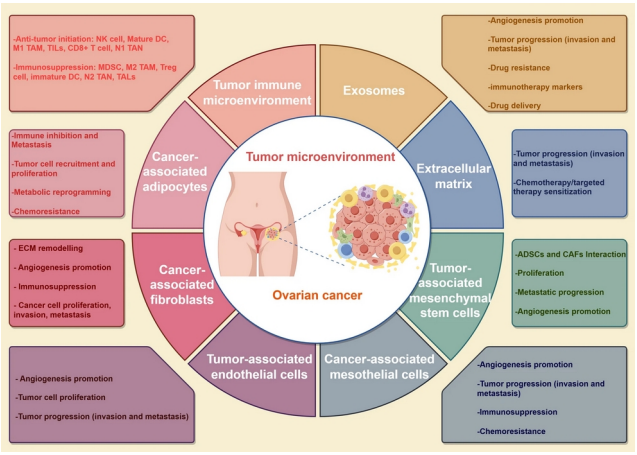


Figure 1.4: Tumor microenvironment modulation and therapeutic resistance in ovarian cancer

Despite ongoing therapeutic advances, approximately 80% of ovarian cancer patients relapse after initial treatment. Roughly 40% of patients don't respond at all to initial therapy or relapse within 6 months of completing therapy. Notably, for patients whose tumors express the endothelin B receptor (ETBR), survival is much worse and the tumors lack the immune cells required for immunotherapy to be effective (Kandalaft et al., 2009).

1.3 Pancreatic Cancer: Epidemiology and Prognosis

Pancreatic cancer remains one of the most lethal malignancies, with a disproportionately high mortality rate relative to its incidence. In the United States, an estimated 67,440 new cases and 51,980 deaths are projected for 2025, highlighting the aggressive nature of the disease. It is currently the third leading cause of cancer-related death among both men and women combined, underscoring its significant clinical and public health burden (SEER, 2025; American Cancer Society, 2024).

Globally, the burden continues to increase, with 508,532 incident cases reported in 2021 and mortality rising substantially from 211,613 deaths in 1990 to 505,752 in 2021 (Li et al., 2024; Global Burden of Disease Study, 2021).

Pancreatic cancer primarily affects older adults, with a median age at diagnosis of approximately 70 years and peak incidence occurring between 65 and 79 years of age. Established risk factors include tobacco use, type 2 diabetes, obesity, chronic pancreatitis, and inherited genetic predisposition, particularly pathogenic variants in *BRCA1* and *BRCA2* (Qadir et al., 2024; Ramai et al., 2024; PMC, 2024).

Despite advances in systemic therapy and supportive care, prognosis remains poor, with an overall 5-year survival rate of approximately 12.8% across all stages. Survival outcomes decline substantially with increasing disease severity, as illustrated in **Figure 1.5**, where patients with higher-grade tumors experience markedly shorter overall survival than those with lower-grade disease. Similarly, **Figure 1.6** demonstrates the profound impact of disease stage at diagnosis and surgical outcomes on long-term survival, with Stage IV disease associated with significantly worse outcomes compared with Stage III disease and with patients who undergo successful surgical debulking.

Poor outcomes in pancreatic cancer are driven in part by a dense, immunosuppressive tumor microenvironment that restricts both therapeutic drug delivery and immune cell infiltration (Park et al., 2021; PMC, 2024).ETBR signaling further promotes immune evasion by limiting T-cell trafficking into tumors, contributing to treatment resistance and supporting its investigation as a potential therapeutic target.

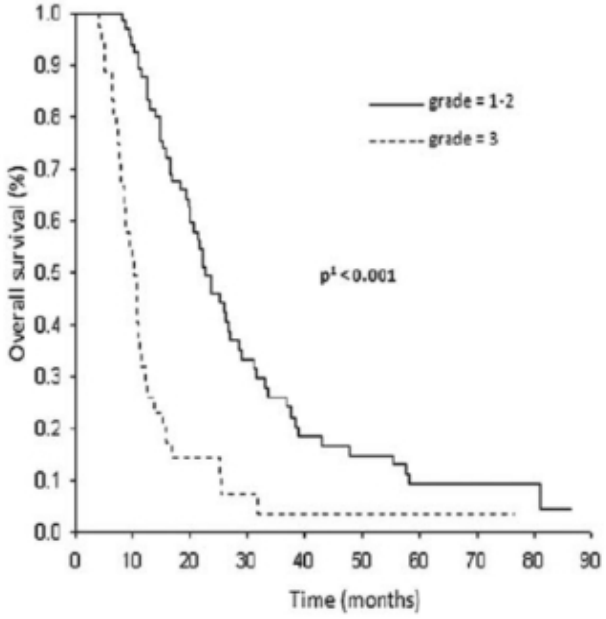


Figure 1.5: Overall survival among patients with pancreatic cancer stratified by tumor grade

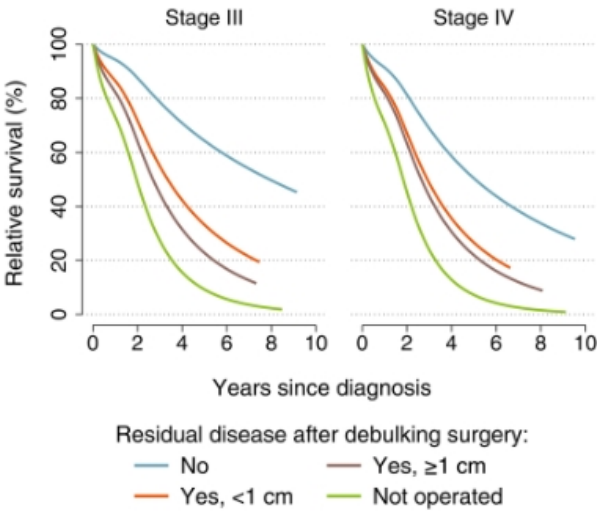


Figure 1.6: Relative survival in pancreatic cancer according to disease stage and residual disease status following surgical debulking

1.4 Broader MSS Solid Tumor Landscape

Microsatellite stable (MSS) tumors present a significant therapeutic challenge across multiple cancer types beyond ovarian and pancreatic cancers. MSS colorectal cancer represents approximately 95% of all colorectal cancer diagnoses—making it the second leading cause of cancer-related mortality worldwide—and is characterized by low tumor mutational burden, limited immune cell infiltration, and an immunosuppressive microenvironment, all of which contribute to resistance to current immunotherapies. Similar MSS profiles are observed in substantial proportions of triple-negative breast cancer (TNBC), head and neck squamous cell carcinoma (HN-SCC), and melanoma, which are key target indications for ENB-003 (Bray et al., 2024; Cancer Cell International, 2026).

ETBR is expressed in more than 40% of all solid tumors and ENB-003 has demonstrated efficacy in MSS solid tumors in a Phase 1 clinical study. This broad expression pattern positions the ENB-003 platform for potential application across a wide oncology landscape far beyond the initial ovarian and pancreatic cancer indications. The following sections detail the biological rationale, the clinical evidence, and the economic implications of addressing ETBR-driven resistance.

Section 2: Immunotherapy Resistance — A Crisis in Modern Oncology

2.1 The Promise and Limits of Immune Checkpoint Inhibitors

The development of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 and CTLA-4 pathways represents one of the most significant advances in oncology over the past two decades. These therapies function by inhibiting key immune checkpoint pathways that tumors exploit to evade immune detection. Specifically, blockade of the interaction between PD-1 receptors on T cells and PD-L1 ligands on tumor cells prevents T-cell exhaustion and restores anti-tumor immune activity in responsive patient populations (Vatsavai et al., 2025; Waldman et al., 2020).
Despite these advances, the overall effectiveness of immunotherapy remains limited across most solid tumors. Clinical evidence indicates that more than 75% do not respond to first-line PD-1/PD-L1 inhibitors. Addressing mechanisms of resistance has therefore emerged as a critical priority. The Society for Immunotherapy of Cancer (SITC) has identified resistance to immunotherapy as a key area requiring urgent research focus, underscoring the significant unmet need in expanding the efficacy of these treatments (SITC, 2024).

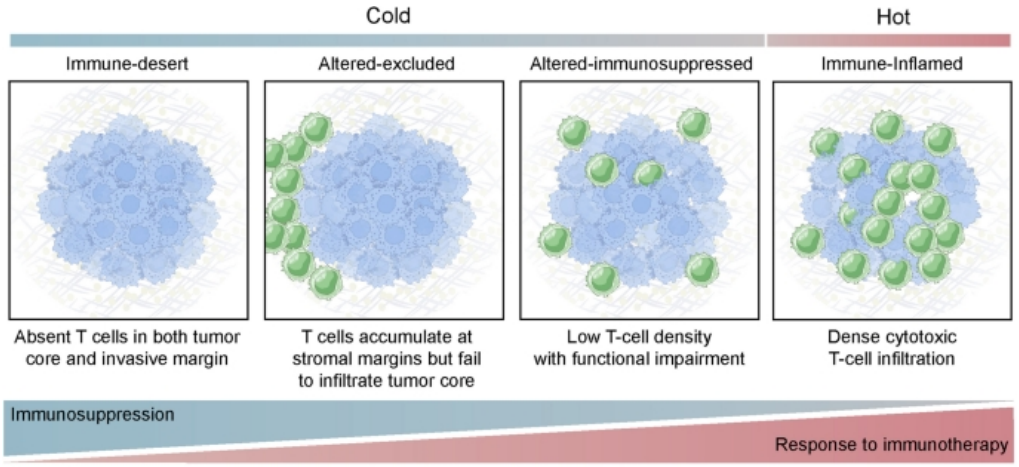


Figure 2.2:Tumor immune phenotypes and their relationship to immunotherapy response

Resistance to immunotherapy in solid tumors is driven by multiple mechanisms within the tumor microenvironment (TME), including impaired antigen presentation, T-cell dysfunction, and immunosuppressive cell populations. As shown in **Figure 2.2**, tumors exist along a spectrum from immune-desert and immune-excluded ("cold") phenotypes to immune-inflamed ("hot") phenotypes, with treatment response generally increasing as T-cell infiltration improves. Physical barriers within the TME, including stromal architecture and abnormal vasculature, further restrict immune cell trafficking and contribute to therapeutic resistance (Yang et al., 2024; TechScience, 2025).

2.3 The Unaddressed Patient Population

Patients with ETBR-expressing MSS tumors represent a large population with limited immunotherapy options. In these tumors, immune cells are often restricted to the tumor periphery rather than infiltrating the tumor core (**Figure 2.2**), resulting in poor antitumor immune activity. This ETBR-driven immune exclusion remains largely unaddressed by currently approved therapies and represents the primary mechanism targeted by ENB-003.

2.4 The Immunotherapy Market and Its Structural Deficiencies

The global cancer immunotherapy market has experienced significant growth, reflecting the increasing adoption of immune-based treatment modalities. Valued at approximately USD 168.1 billion in 2024, the market is projected to reach USD 314.4 billion by 2033, representing a compound annual growth rate (CAGR) of 7.2%. Key segments driving this growth include monoclonal antibodies, immune checkpoint inhibitors, cancer vaccines, and adoptive cell therapies. However, despite the scale and expansion of this market, a substantial proportion of patients remain non-responsive to current therapies. This persistent limitation highlights the critical need for biomarker-guided patient selection strategies, and the development of novel therapeutic approaches capable of overcoming immune exclusion and resistance mechanisms (Custom Market Insights, 2026).

Earlier Attempts at ETBR Blockade Failed: The Bosentan Lessons

Early ETBR targeting with Bosentan failed due to mechanistic misinterpretation but informed next-generation therapies such as ENB-003, highlighting the need for drugs that are selective for the ETBR receptor.

Bosentan is a potent endothelin A receptor (ETAR) antagonist (IC_{50} 4.7 nM) but a relatively weak ETBR antagonist (IC_{50} 95 nM). Importantly**, selective ETBR blockade promotes T-cell trafficking into tumors by overcoming endothelial barriers to immune cell infiltration, whereas dual A/B blockade does not.** As illustrated in **Figure 2.3**, ETBR signaling interferes with a critical step in the cancer immunity cycle—the migration of effector T cells into the tumor microenvironment. Consequently, selective ETBR inhibitors such as ENB-003 may convert immunologically "cold" tumors into more immune-permissive states, whereas non-selective agents such as Bosentan have demonstrated limited clinical benefit.

Subsequent studies demonstrated that melanoma cells produce high levels of ET-1 and ET-3, creating an autocrine signaling loop that promotes ETBR activation. Bosentan was not optimized to effectively disrupt this biology, owing to its limited receptor selectivity, competitive binding profile, and short receptor residence time.

Together, these factors likely contributed to its lack of clinical efficacy and informed the development of more selective next-generation ETBR inhibitors (Coffman et al., 2013; Clinical Pharmacology & Therapeutics, 1996; British Journal of Pharmacology).

While immuno-oncology continues to advance through novel checkpoint targets such as TIGIT and TIM-3, many approaches do not address the upstream barrier of immune cell trafficking into tumors. As shown in **Figure 2.3**, ETBR inhibition targets this critical bottleneck by facilitating T-cell infiltration, potentially enhancing the effectiveness of existing immunotherapies.

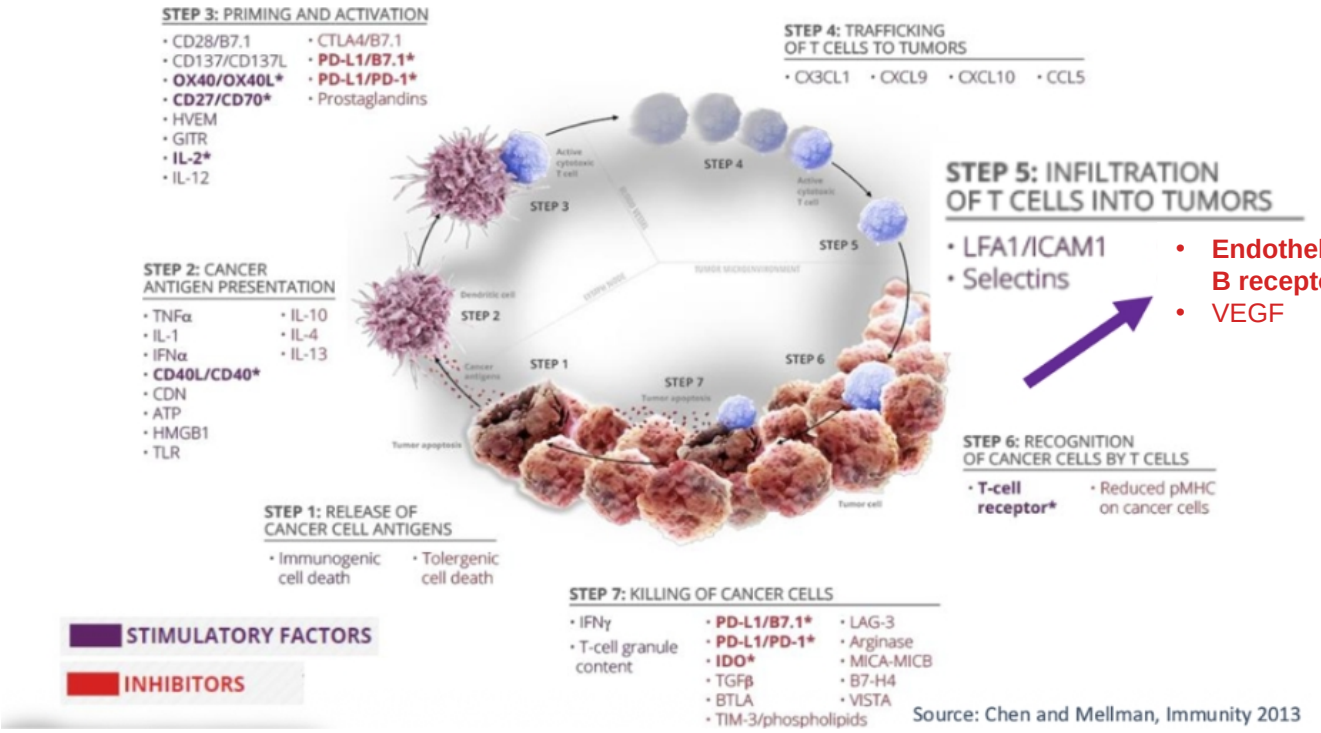


Figure 2.3: ETBR-mediated inhibition of T-cell trafficking within the cancer immunity cycle

Section 3: The Tumor Microenvironment and Immune Exclusion

3.1 The Tumor Microenvironment: Architecture of Resistance

The tumor microenvironment (TME) is a complex and dynamic ecosystem composed of malignant cells, stromal cells, immune cells, and extracellular matrix components that interact through a network of cytokines, metabolites, and signaling pathways. As illustrated in **Figure 3.1**, these cellular and molecular interactions create a highly heterogeneous environment that actively promotes immune evasion, tumor progression, and therapeutic resistance.

The progression of solid tumors is governed by continuous crosstalk between malignant cells and the surrounding microenvironment. Immune checkpoint inhibitors (ICIs) enhance antitumor immunity by restoring T-cell activity, particularly through the PD-1/PD-L1 pathway. However, their effectiveness is frequently limited by TME-mediated resistance mechanisms.

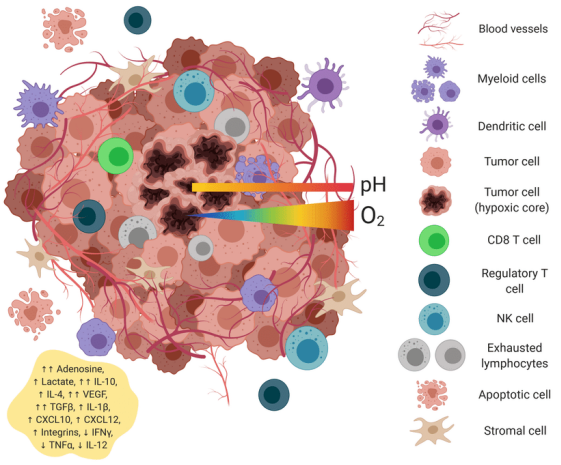


Figure 3.1: Cellular and molecular components of the tumor microenvironment.

Among these, the immunosuppressive characteristics of "cold" tumors—including poor immune infiltration and inhibitory signaling—play a central role in both primary and acquired resistance to ICIs (TechScience, 2025; Vasilieva et al.).

ETBR Drives Three Core Immunosuppressive Processes in the TME

- Blocking immune cell trafficking resulting in “cold tumors”
- CAF and TAM activation — promoting desmoplasia and pro-tumoral macrophage polarisation
- Tumor invasion and metastasis — via autocrine ET-1/ETBR signalling on tumor cells

3.2 The Vascular Barrier: T-Cell Exclusion at the Endothelium

The tumor vasculature represents a critical, yet often underappreciated, barrier to effective antitumor immunity. Successful immune responses require T cells to adhere to and migrate across the tumor endothelium, a process dependent on endothelial adhesion molecules such as ICAM-1.

In many immunologically "cold" tumors, this trafficking process is impaired, resulting in limited tumor-infiltrating lymphocytes despite the presence of systemic antitumor immune responses. This vascular barrier represents one of the key mechanisms by which the TME maintains immune exclusion and therapeutic resistance.

A landmark study by Buckanovich et al. (2008) identified a key mechanism underlying immune exclusion in ovarian cancer. Through transcriptional profiling of microdissected tumor endothelial cells, the authors demonstrated that endothelin B receptor (ETBR) overexpression was associated with reduced tumor-infiltrating lymphocyte (TIL) density and poorer clinical outcomes.

Mechanistically, ET-1-mediated ETBR activation suppressed ICAM-1 expression through nitric oxide signaling, impairing T-cell adhesion and transendothelial migration. These findings established the tumor endothelium as a critical regulator of immune cell trafficking and identified ETBR as a promising therapeutic target for overcoming immune exclusion.

ETBR as a Therapeutic Target for Immunotherapy

Subsequent research has expanded the understanding of ETBR biology, demonstrating that ETBR contributes to immune evasion across multiple tumor types. Elevated ETBR signaling has been associated with reduced TIL infiltration, resistance to immunotherapy, and poor clinical outcomes, supporting its role as a key mediator of immune exclusion.

Key findings include:

- ETBR-associated gene signatures have been linked to innate resistance to anti-PD-1 therapy and acquired resistance to MAPK-targeted therapies.
- Preclinical studies demonstrate that ETBR blockade enhances TIL recruitment and improves responses to immunotherapy.
- In contrast, ETAR blockade suppresses TIL extravasation, underscoring the importance of selective ETBR targeting.
- Collectively, these findings support combining ETBR inhibition with existing immunotherapies to improve immune infiltration, overcome resistance mechanisms, and enhance treatment efficacy.

3.3 Cancer-Associated Fibroblasts and Tumor-Associated Macrophages

Beyond the endothelial barrier, the immunosuppressive tumor microenvironment is reinforced by stromal and immune cell populations, particularly cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs). CAFs contribute to extracellular matrix deposition and desmoplasia, creating physical barriers that impede immune cell infiltration. TAMs frequently adopt an immunosuppressive phenotype that suppresses cytotoxic T-cell and natural killer (NK) cell activity, promoting tumor progression.

ETBR signaling contributes to both CAF-driven stromal remodeling and TAM polarization. ETBR expression on CAFs promotes fibrosis and the development of an immune-excluded microenvironment, while signaling in TAMs supports pro-tumor macrophage activity and limits effective immune surveillance.

Section 4: The Endothelin-B Receptor (ETBR) — A Comprehensive Literature Review

4.1 The Endothelin System: Biological Background

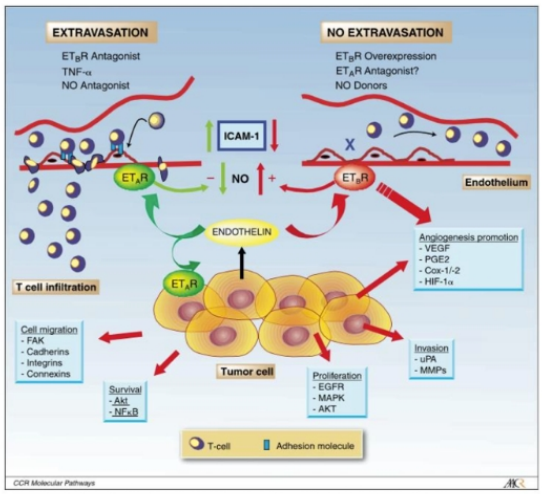
The endothelin system is a complex signaling network comprising four peptide ligands (ET-1, ET-2, ET-3, and ET-4), two G protein-coupled receptors—endothelin A receptor (ETAR) and endothelin B receptor (ETBR)—and endothelin-converting enzymes (ECEs), which generate biologically active endothelins. Among these ligands, ET-1 is the predominant isoform and is produced primarily by endothelial cells. Through autocrine and paracrine signaling, ET-1 regulates vascular tone, endothelial function, and cellular proliferation by binding to ETAR and ETBR on endothelial cells, pericytes, and vascular smooth muscle cells.

Dysregulation of endothelin signaling has been implicated in numerous pathological conditions, including pulmonary hypertension and cancer (Levin, 1996; D'Orleans-Juste et al., 2002; Buckanovich et al., 2009). Although ETAR and ETBR share a common ligand, they mediate distinct and often opposing biological effects. ETAR, predominantly expressed on tumor cells, promotes cellular proliferation, migration, invasion, and survival and has historically been the primary focus of endothelin-targeted drug development.

In contrast, ETBR is highly expressed on tumor-associated endothelial cells and plays a central role in regulating immune cell trafficking within the tumor microenvironment. ETBR activation suppresses expression of intercellular adhesion molecule-1 (ICAM-1), thereby limiting T-cell adhesion and extravasation into tumors. In addition to its role in immune exclusion, ETBR signaling has been implicated in tumor invasion and metastasis. **These findings position ETBR as a key regulator of immune evasion and therapeutic resistance within the tumor microenvironment** (Buckanovich et al., 2009; *Clinical Cancer Research*).

4.2 ETBR in Tumor Vasculature: The Foundational Studies

The seminal work establishing ETBR as a novel immune checkpoint was published by Buckanovich et al. in *Nature Medicine* (2008). Through transcriptional profiling of microdissected tumor endothelial cells from human ovarian cancers, the authors identified ETBR as a key mediator of endothelial immune exclusion. As illustrated in **Figure 4.1**, ETBR signaling suppresses T-cell trafficking across the tumor endothelium, thereby limiting immune infiltration into the tumor microenvironment.



Kandalaft et al., Clin Cancer Res 2009;15(14) July 15, 2009

Figure 4.1: ETBR- mediated mechanisms of tumor immune evasion and T Cell exclusion.

The study demonstrated that ETBR overexpression was strongly associated with reduced tumor-infiltrating lymphocyte (TIL) density and poorer survival in patients with advanced epithelial ovarian cancer. Mechanistically, ET-1-mediated activation of ETBR suppressed endothelial ICAM-1 expression through a nitric oxide-dependent pathway, impairing T-cell adhesion and transendothelial migration.

Subsequent functional studies validated this mechanism. Pharmacologic inhibition of ETBR using BQ-788 restored T-cell adhesion to tumor endothelial cells in vitro and enhanced T-cell homing to tumors in murine models. Notably, these effects occurred without inducing systemic immune activation, highlighting the localized role of endothelial ETBR signaling in regulating immune cell trafficking (Buckanovich et al., 2008). Consistent with these observations, **Figure 4.2** demonstrates the association between elevated ETBR expression, reduced TIL infiltration, and poorer clinical outcomes in ovarian cancer.

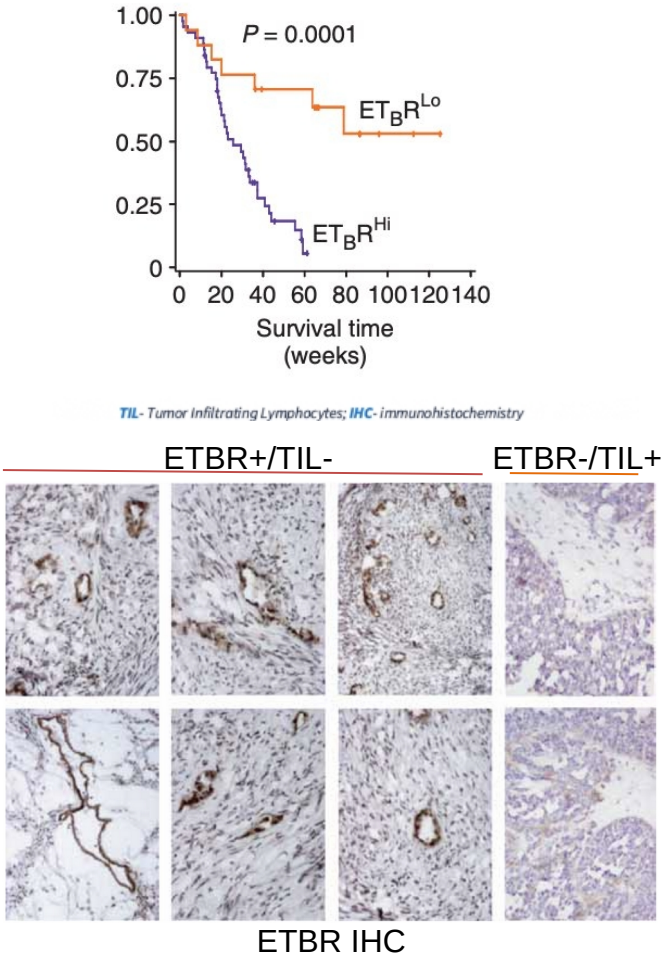


Figure 4.2: Association of ETBR expression with reduced TIL infiltration and poorer survival in ovarian cancer

4.3 Independent Validation Across Multiple Cancer Types

Subsequent studies have validated ETBR as a mediator of tumor immune exclusion across multiple cancer types. In pancreatic ductal adenocarcinoma (PDAC), ETBR signaling contributes to an immunosuppressive microenvironment by limiting $CD8^+$ T-cell infiltration and reinforcing endothelial barriers to immune cell trafficking. Preclinical studies suggest that ETBR inhibition can restore T-cell infiltration and improve responses to immunotherapy.

Similar associations have been reported in other malignancies. In oesophageal squamous cell carcinoma, high ETBR expression was associated with poorer overall and disease-specific survival and increased microvessel density, supporting a role in angiogenesis and tumor progression (Enomoto et al., 2014). In glioma and glioblastoma, elevated ETBR expression has been linked to reduced $CD8^+$ T-cell infiltration, increased regulatory T-cell populations, and poorer clinical outcomes (Nakashima et al., 2016).

Evidence from primary CNS lymphoma further suggests that ETBR expression within the tumor vasculature may contribute to immune exclusion by restricting lymphocyte trafficking across the blood-brain barrier. Collectively, these findings support a conserved role for ETBR in regulating immune cell access to tumors across diverse cancer types.

4.4 ETBR as a Predictor of Anti-PD1 Non-Response: 2024 JEM Study

The strongest recent validation of ETBR as a driver of immunotherapy resistance was reported in a 2024 study published in the *Journal of Experimental Medicine*. **Analysis of more than 10,000 tumors from The Cancer Genome Atlas (TCGA) identified ETBR expression as one of the strongest predictors of resistance to anti-PD-1 therapy**, outperforming established biomarkers including PD-1, PD-L1, and CTLA-4. **Among immunologically "cold" tumors, ETBR emerged as the biomarker most strongly associated with checkpoint inhibitor failure, further supporting its central role in immune exclusion** (Journal of Experimental Medicine, 2024).

Beyond its biological significance, ETBR may also have clinical utility as a predictive biomarker. Measurement of ETBR expression could help identify patients less likely to respond to current checkpoint inhibitors and support treatment stratification strategies. The association between elevated ETBR expression and poorer survival outcomes, illustrated in **Figure 4.4**, further highlights its potential relevance for patient selection and targeted therapeutic development.

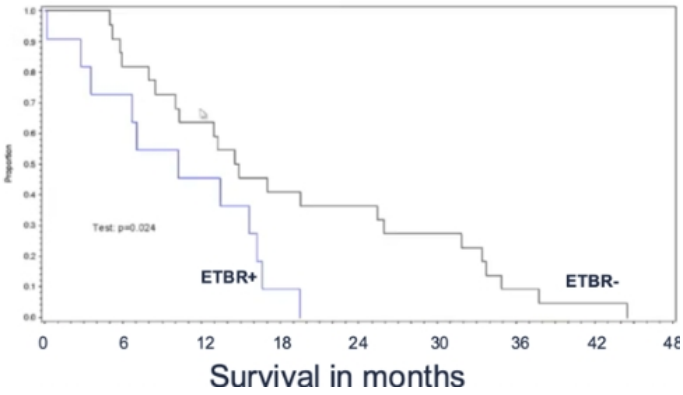


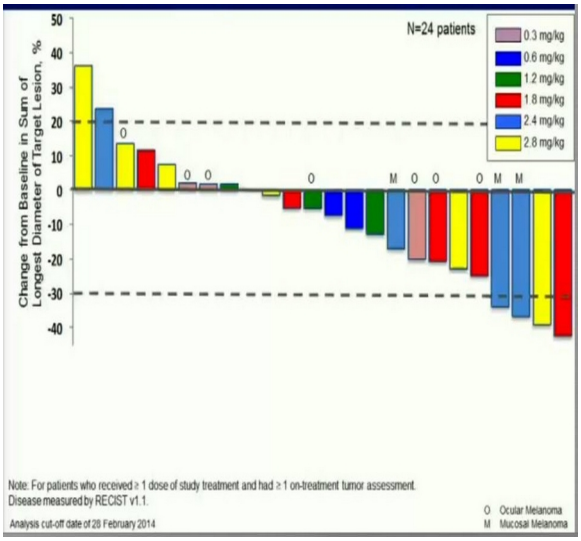
Figure 4.4: Association between elevated ETBR expression and reduced overall survival in pancreatic cancer

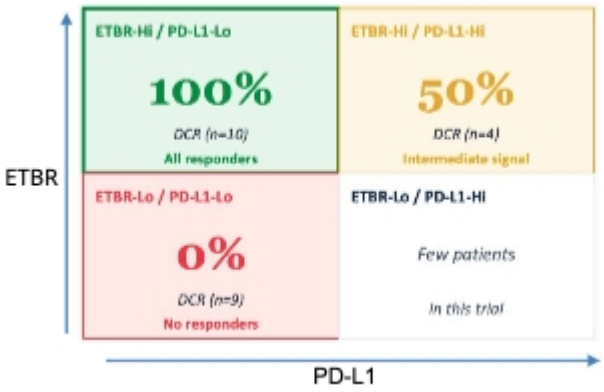
Key Biomarker Insight: ETBR-Hi / PD-L1-Lo Patients treated with ENB-003 combination demonstrate 100% disease control rate

- ETBR-high expression identifies the immune-excluded patient population that ENB-003 targets
- PD-L1-low expression confirms these patients are not candidates for standard checkpoint inhibitor monotherapy
- This combination biomarker profile enables precise patient selection and maximises therapeutic benefit
- A companion diagnostic for ETBR expression is central to the ENB-003 clinical development strategy

4.5 Roche-Genentech Independent Validation

Independent pharmaceutical validation further supports endothelin B receptor (ETBR) as a clinically relevant therapeutic target. Roche-Genentech developed an ETBR-targeted antibody-drug conjugate (ADC), which demonstrated measurable clinical activity in a Phase 1 study of patients with drug-resistant melanoma. As shown in **Figure 4.6**, objective tumor reductions were observed across multiple dose levels, with partial





responses reported in 11% of patientsand prolonged stable disease achieved in32% (n = 53). Although the ADC wasevaluated as monotherapy and not incombination with immunotherapy, these findings provided independent clinical validation that ETBR can be successfully targeted in cancer patients.

Additional studies have shown that ETBR upregulation contributes to acquired resistance to BRAF inhibitors, suggesting a broader role in treatment resistance beyond immunotherapy. Collectively, these findings support ETBR as a clinically relevant target across multiple therapeutic modalities and tumor types (Infante et al., 2014).

4.6 The ET-1/ETBR Signalling Loop: Tumor Progression Beyond Immune Exclusion

Beyond its role in immune exclusion, the endothelin-1 (ET-1)/ETBR signaling axis contributes directly to tumor progression through multiple mechanisms within the tumor microenvironment. In tumor cells, ETBR activation promotes proliferation, migration, invasion, and extravasation, facilitating metastatic dissemination. These observations suggest that **ETBR inhibition may provide dual therapeutic benefit by both enhancing antitumor immunity and suppressing tumor-intrinsic pathways associated with disease progression.**

Figure 4.6: Clinical activity of an ETBR-targeted antibody-drug conjugate in a Phase 1 melanoma study

Notably, ETBR expression has been shown to increase with disease progression and is associated with increasingly aggressive and immunosuppressive tumor phenotypes. In parallel, ETBR signaling within cancer-associated fibroblasts (CAFs) promotes desmoplasia and vascular remodeling, while activity in tumor-associated macrophages (TAMs) supports immunosuppressive polarization and contributes to treatment resistance (PMC, 2024; Voutouri et al., 2021).

Collectively, these findings highlight the multifaceted role of ETBR within the tumor microenvironment. Beyond regulating immune cell trafficking, ETBR influences stromal remodeling, macrophage polarization, tumor invasion, and metastatic progression. The breadth of these biological effects underscores its potential relevance as a therapeutic target in cancers characterized by immune exclusion and treatment resistance.

Section 5: Clinical and Economic Burden of Drug-Resistant Cancers

5.1 The Cost of Ovarian Cancer

Ovarian cancer imposes a substantial economic burden, driven by high treatment costs, late-stage diagnosis, and frequent disease recurrence. Healthcare expenditures are often concentrated at treatment initiation and the end of life, while the cost-effectiveness of existing therapies may remain limited.

Some treatments have been reported to exceed commonly accepted willingness-to-pay thresholds, with incremental cost-effectiveness ratios approaching or exceeding CAD$200,000 per quality-adjusted life year (QALY), reflecting a mismatch between high costs and modest clinical benefit (Bonilla-Bernal et al., 2018).

ETBR's Multi-Compartmental Role in Tumor Progression

- Activates cancer-associated fibroblasts (CAFs) → promotes desmoplasia and physical immune barriers
- Activates tumor-associated macrophages (TAMs) → drives pro-tumoral, immunosuppressive M2 polarisation
- Drives immunosuppression through TME remodelling and ICAM-1 downregulation
- Promotes invasion and metastasis through autocrine ET-1/ETBR signalling on tumor cells
- ETBR expression increases with disease progression — compounding resistance and aggressive tumor behavior

This burden is further amplified by disease progression patterns. More than 70% of patients with advanced ovarian cancer experience recurrence, often requiring multiple lines of therapy, repeated hospitalizations, and ongoing supportive care, all of which contribute to rising healthcare utilization and costs (Harrison et al., 2024; PMC10391014).

Furthermore, over half of patients are diagnosed with advanced-stage disease, increasing treatment complexity and resource requirements.

Collectively, these factors make ovarian cancer one of the most resource-intensive gynecologic malignancies. The high rates of recurrence and progression highlight the need for therapies capable of improving disease control and achieving more durable responses earlier in the treatment course.

5.2 The Cost of Pancreatic Cancer

Pancreatic cancer imposes a substantial economic burden in addition to its significant clinical impact. Direct healthcare costs are particularly high due to the need for complex, specialized treatments, often initiated at advanced stages of disease. Indirect costs—including loss of workforce productivity and caregiver burden—further contribute to the overall societal impact. Economic projections suggest that this burden will continue to rise through at least 2030, driven by increasing incidence and persistently poor outcomes (Draus et al., 2021; Luo et al., 2023).

In the United States, progression from localized to metastatic pancreatic cancer is associated with a marked increase in healthcare expenditures compared with individuals without cancer. These findings underscore the economic value of interventions that delay disease progression and improve disease control. Therapies capable of extending progression-free survival may not only improve patient outcomes but also reduce downstream healthcare utilization and associated costs (Tomso et al., 2005).

5.3 The Hidden Costs of Failed Immunotherapy

The economic burden of immunotherapy resistance extends beyond the direct costs of unsuccessful treatment. Patients who do not respond to checkpoint inhibitors frequently require additional lines of therapy, increased monitoring, management of immune-related adverse events (irAEs), hospitalization for disease progression, and supportive or palliative care. Indirect costs associated with reduced productivity, caregiver burden, and diminished quality of life further increase the overall burden.

The financial implications are particularly significant given the high cost of modern immunotherapies. For example, pembrolizumab (Keytruda) has a list price exceeding $200,000 per year in the United States. Consequently, treatment of patients who are unlikely to respond can result in substantial healthcare expenditures without meaningful clinical benefit. These challenges highlight the importance of predictive biomarkers and patient selection strategies that improve treatment allocation and maximize clinical value.

A companion diagnostic for ETBR expression — already in development by ENB Therapeutics — represents a potential solution to this inefficiency. By identifying ETBR-High patients most likely to benefit from ENB-003, the companion diagnostic could substantially improve the cost-effectiveness of immunotherapy in the drug-resistant solid tumor population, reducing wasteful expenditure on ineffective treatments.

5.4 Quality of Life Burden

Beyond direct healthcare expenditures, drug-resistant cancers impose a substantial quality-of-life burden on patients and caregivers. Individuals with treatment-refractory disease often undergo multiple lines of therapy with diminishing clinical benefit while experiencing cumulative toxicities, including fatigue, immune suppression, neuropathy, nausea, and other treatment-related adverse effects. The physical burden of progressive disease is frequently compounded by psychological distress and declining functional status. As treatment options become increasingly limited, preserving quality of life becomes an important therapeutic objective alongside disease control.

ENB-003's subcutaneous route of administration and favorable early safety profile may offer practical advantages compared with more intensive treatment approaches. In Phase 1 studies, no dose-limiting toxicities were reported, and adverse events were generally manageable. The ability to administer treatment in outpatient settings may reduce both patient burden and healthcare resource utilization relative to therapies requiring prolonged infusion or inpatient care.

Collectively, the scientific, clinical, and economic evidence supporting ETBR as a therapeutic target has provided the foundation for the development of selective ETBR inhibitors, including ENB-003.

Section 6: About ENB Therapeutics

6.1 Company Overview

ENB Therapeutics is a clinical-stage oncology biotechnology company focused on developing therapies that target endothelin B receptor (ETBR)-mediated immune exclusion. The company's lead candidate, ENB-003, is a selective ETBR inhibitor being evaluated in combination with anti-PD-1 therapy for platinum-resistant ovarian cancer and chemoresistant pancreatic cancer.

The program is based on the hypothesis that selective ETBR inhibition can enhance immune cell infiltration and improve responses to immunotherapy in tumors characterized by immune exclusion.

6.2 Strategic Positioning

Selective ETBR inhibition represents a novel therapeutic approach targeting immune exclusion, a mechanism implicated in resistance to immunotherapy across multiple solid tumor types. To date, no approved therapies directly target ETBR-mediated regulation of T-cell trafficking within the tumor microenvironment.

ENB Therapeutics is developing its ETBR inhibitor platform to address several unmet needs in oncology. First, most microsatellite-stable (MSS) solid tumors, including ovarian and pancreatic cancers, derive limited benefit from currently approved immunotherapies. Second, no approved therapies directly target the endothelial barrier that restricts T-cell trafficking into tumors. Third, the absence of validated biomarkers for identifying patients with immune-excluded tumors remains a challenge for treatment selection.

The company's strategy combines selective ETBR inhibition with biomarker-guided patient identification, with the goal of improving immune infiltration and enhancing responsiveness to existing immunotherapies in tumors characterized by immune exclusion.

6.3 The Leadership Team

The ENB Therapeutics leadership team combines expertise in oncology drug development, biotechnology commercialization, regulatory strategy, and clinical operations.

Collectively, the team has participated in numerous therapeutic development programs spanning discovery, clinical development, regulatory approval, and commercialization.
The scientific leadership includes researchers with deep expertise in ETBR biology and translational oncology, providing continuity from the foundational discoveries that established ETBR as a therapeutic target through the development of ENB-003.

This combination of scientific insight and operational experience positions the company to efficiently advance its clinical programs and execute its broader platform strategy.

Team Member	Role	Key Experience
Sumayah Jamal, MD-PhD 	CEO / CSO / Co-Founder	Physician scientist, pioneer in the endothelin field, research career spanning over 30 years. Co-inventor on the first patents filed covering the ETBR as a therapeutic target for cancer. She has taken the company through a venture backed Series A round, entered into two collaborations with big pharma and completed a successful Phase 1 clinical trial. Raised $23M to date
Robert J. Schneider, PhD 	Co-Founder / SAB Chair	Senior scientist at NYU School of medicine, co-founded seven successful biotech companies including Imclone. Led tech transfer initiatives at NYU School of Medicine
Sandy Harm, MBA 	Chief Operating Officer	Senior exec. at Merck for 24 years. Served as US Oncology, Director of Commercial Operations and oversaw the development and launch of Merck's blockbuster drug Keytruda.
Giovanni Selvaggi, MD 	Acting CMO	Clinical oncologist, seasoned drug developer, 15+years industry experience leading Phase I-III clinical trials and IND/NDA filings

Section 7: The ENB-003 Platform — Mechanism and Drug Properties

7.1 Overview: A New Drug Class in Oncology

ENB-003 (vodudonertan) is a first-in-class, selective small-molecule inhibitor of the endothelin B receptor (ETBR) designed to overcome tumor immune exclusion. Unlike conventional immunotherapies that act downstream by enhancing T-cell activation, ENB-003 targets an upstream mechanism of resistance by restoring immune cell access to the tumor microenvironment.

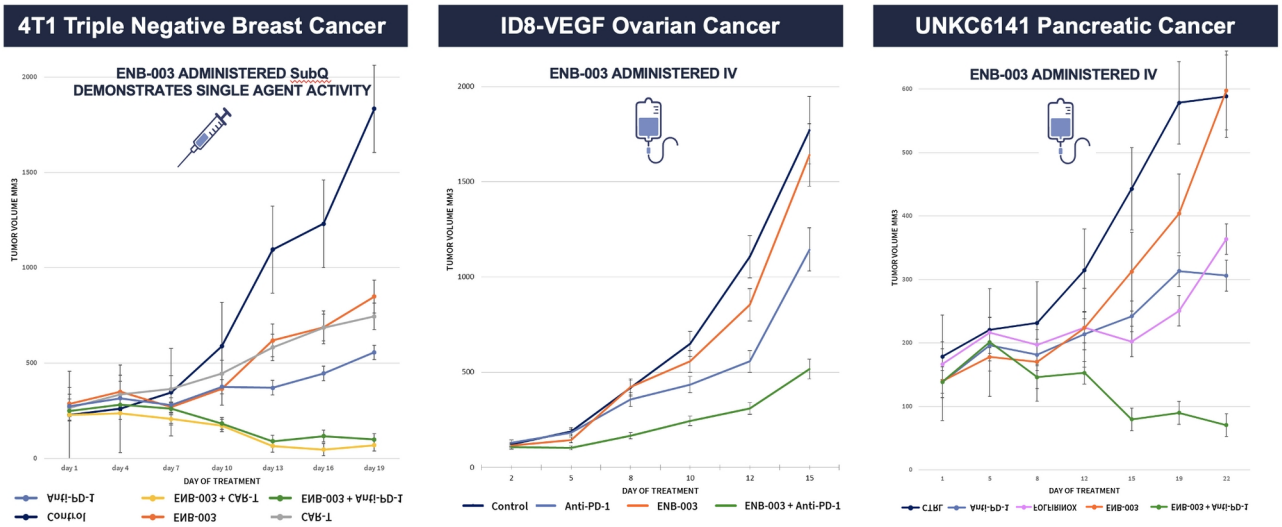
Many solid tumors remain immunologically "cold," characterized by limited tumor-infiltrating lymphocyte (TIL) density despite intact systemic immunity. This phenotype is driven in part by ETBR-mediated suppression of endothelial adhesion molecules, including ICAM-1, which are required for T-cell adhesion and transendothelial migration into tumor tissue (Buckanovich et al., 2008). By selectively inhibiting ETBR, ENB-003 removes this endothelial barrier and promotes immune cell infiltration into previously immune-excluded tumors.

Importantly, ENB-003 was specifically designed to preserve ETAR signaling while selectively inhibiting ETBR. This distinction differentiates it from earlier endothelin receptor antagonists such as bosentan, whose non-selective inhibition of both ETAR and ETBR impaired T-cell trafficking and likely contributed to limited clinical efficacy (Voutouri et al., 2021). **The selectivity profile of ENB-003 therefore addresses a key limitation of prior approaches targeting the endothelin pathway.**

Consistent with its proposed mechanism, ENB-003 demonstrated antitumor activity across multiple preclinical models, including triple-negative breast, ovarian, melanoma, bladder and pancreatic cancers (**Figure 7.1**). These findings support the hypothesis that selective ETBR inhibition may enhance antitumor immunity across diverse solid tumor types.

Collectively, these data position ENB-003 as a novel immunomodulatory therapy designed to enhance immune cell trafficking and potentially improve responsiveness to existing immunotherapies.

Figure 7.1: Antitumor activity of ENB-003 across preclinical solid tumor models



7.2 Multi-Compartmental Mechanism of Action

A defining feature of ENB-003 is its multi-compartmental mechanism of action, targeting multiple biological processes simultaneously within the tumor microenvironment. This distinguishes it from most oncology therapies, which typically act on a single pathway or cell type.

1. Vascular Compartment: Restoration of Immune Trafficking

ETBR activation suppresses ICAM-1 expression, limiting T-cell trafficking across the tumor endothelium. ENB-003 restores immune cell infiltration by reversing this effect (Buckanovich et al., 2008).

Enhanced immune trafficking increases tumor-infiltrating lymphocytes (TILs), promotes tertiary lymphoid structure (TLS) formation, and may improve antitumor immunity (Teillaud et al., 2024).

2. Tumor Cell Compartment: Disruption of Autocrine Signaling and Metastasis

Within tumor cells, ETBR participates in an endothelin-1 (ET-1)-driven autocrine signaling loop that promotes invasion, migration, and metastasis. ENB-003 disrupts this pathway, reducing tumor progression, particularly in advanced cancers where ETBR expression is frequently upregulated (PMC11130555, 2024).

By targeting both immune exclusion and tumor progression, ENB-003 addresses two key drivers of poor clinical outcomes.

3. Stromal and Immune Compartment: Reversal of Immunosuppression

ETBR activation stimulates CAFs to secrete fibrotic extracellular matrix that promotes drug resistance and enhances the immunosuppressive activities of TAMs (Arndt, et al., 2024).

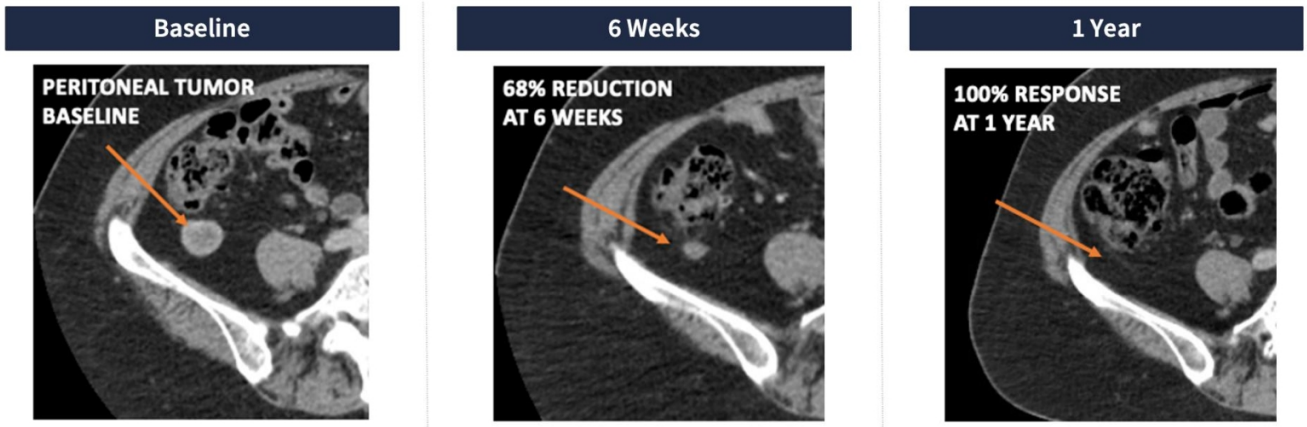


Figure 7.2: Durable radiographic response following treatment with ENB-003 and pembrolizumab in a patient with MSS, platinum-refractory, PD-L1-negative ovarian cancer. A large tumor decreased by 68% after six weeks, was undetectable at 12 weeks and remained undetectable at 12 months. Overall, the patient had a 95% partial response that was durable out to a year.

ENB-003 inhibits these processes, leading to:

- Reduced extracellular matrix density
- Improved immune cell penetration
- Reprogramming of the TME toward an immunostimulatory state

This broad TME remodeling effect explains the synergy observed between ETBR inhibition and immunotherapies including checkpoint inhibitors, CAR-T and cancer vaccines.

Integrated Effect: Conversion of "Cold" Tumors to "Hot" Tumors

Through its combined actions across vascular, tumor, and stromal compartments, ENB-003 effectively reprograms the tumor microenvironment, transforming immune-excluded tumors into immune-responsive ones. This multi-layered mechanism represents a fundamental shift from single-target therapies toward systems-level modulation of tumor biology.

ENB-003 acts simultaneously across three major compartments of the tumor microenvironment:

Compartment	Mechanism	Clinical Consequence
Tumor Blood Vessels	Restores ICAM-1 expression; stimulates T-cell & B-cell infiltration; induces intratumoral TLO formation	Converts immunologically cold tumors to hot; restores immune surveillance
Tumor Cells	Inhibits ETBR-mediated invasion; blocks ETBR-driven metastasis; disrupts autocrine ET-1/ETBR loop	Reduces metastatic potential; suppresses autocrine tumor progression signalling
Immunosuppressive Cells	Blocks CAF-mediated checkpoint resistance; inhibits TAM immunosuppressive function; reduces desmoplasia	Dismantles stromal barriers to immune infiltration; enhances cytotoxic T-cell and NK function

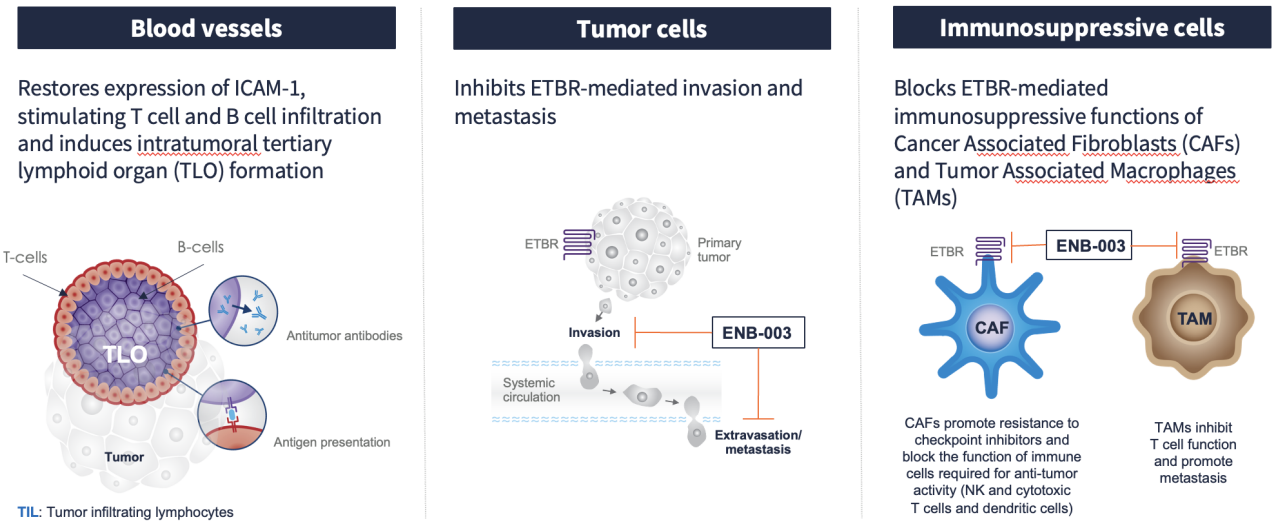


Figure 7.3: ET-1/ETBR signalling loop — multi-compartmental effects driving immunosuppression, invasion, and metastasis

7.3 Key Drug Properties

ENB-003 is a small-molecule therapeutic with pharmacological characteristics optimized for both efficacy and scalability.

Key properties include:

- High selectivity for ETBR, with negligible ETAR inhibition at clinical concentrations (Eurofins Cerep profiling)
- Sustained receptor residence time
- Favorable pharmacokinetics, including 100% bioavailability for both IV and subcutaneous administration
- Importantly, ENB-003 demonstrates an exceptional safety profile, with:
    - No dose-limiting toxicities across six Phase 1 cohorts (N=46)
    - Favorable tolerability compared to cytotoxic chemotherapy
- From a commercial perspective, ENB-003 offers:
    - Low cost of goods (~$240–$250 per dose)
    - Scalable GMP manufacturing
    - Strong intellectual property protection through 2039
- These attributes collectively position ENB-003 as both clinically and economically viable.

Property	Detail
Modality	Small molecule (selective ETBR inhibitor)
Route of Administration	Subcutaneous (SC) and intravenous (IV); 100% bioavailability for both routes
Mechanism	Competitive ETBR inhibition; IC50 = 9.8 x 10-8 M; ETBR inhibition duration >48 hours
Selectivity	Highly selective for ETBR; ETAR inhibition undetectable at clinical concentrations
Cost of Goods	~$240–$250 per dose (commercially scalable GMP manufacturing)
Patent Protection	Issued composition of matter & method of use patents; key expiry 2039 (100% company-owned)
Toxicology	NOAEL at all GLP and non-GLP tox doses across two species
Manufacturing	GMP drug substance/ drug product, >95% purity; 4-year stability at 2–8°C

7.4 Formulation Discovery: The Subcutaneous Advantage

A critical innovation in ENB-003 development is the optimization of its subcutaneous formulation, providing significant PK advantages over intravenous administration.

While IV dosing results in rapid peak concentration followed by decline, SC administration enables:

- Prolonged time above IC50
- Sustained receptor inhibition within the tumor microenvironment
- Enhanced therapeutic exposure

This enhanced exposure results in a profound increase in the single agent activity of ENB-003.
From a clinical perspective, SC administration offers several advantages:

- Enables outpatient treatment
- Reduces infusion-related burden
- Improves patient adherence and quality of life

These benefits align with broader trends toward decentralized, patient-centric oncology care.

7.5 Strategic Differentiation in Oncology Landscape

ENB-003 occupies a uniquely differentiated position in oncology due to its ability to address a previously untargeted mechanism of immunotherapy resistance.

Key differentiators include:

- First therapy to target ETBR-mediated immune exclusion
- Activity in MSS tumors and PD-L1-Lo tumors, where checkpoint inhibitors are largely ineffective
- Multi-compartment mechanism addressing vascular, tumor, and stromal biology
- Biomarker-driven patient selection via ETBR/PD-L1 profiling
- Compatibility with multiple therapeutic modalities (checkpoint inhibitors, CAR-T, vaccines)

This positioning allows ENB-003 to function not only as a standalone therapy but also as a platform technology capable of enhancing the efficacy of existing treatments across oncology.

Section 8: Clinical Evidence

8.1 Phase 1 — ENBOLDEN-101: Overview

The ENBOLDEN-101 Phase 1 trial established both safety and early efficacy of ENB-003 in a heavily pre-treated, Standard of Care-refractory patient population. Across six dose-escalation cohorts (150 µg to 2,000 µg), a total of 46 patients were treated with ENB-003 in combination with pembrolizumab, providing a robust dataset for evaluating clinical activity in populations with historically poor outcomes.

8.2 Key Phase 1 Efficacy Findings

A key finding from the Phase 1 study was the achievement of sustained systemic exposure above the IC_{50} threshold at the 2000ug dose cohort, supporting prolonged target inhibition. Across all 46 treated patients, ENB-003 demonstrated a favorable tolerability profile while maintaining biologically active exposure levels consistent with its proposed mechanism of action.

This finding is particularly significant in the context of oncology drug development, where toxicity often limits dosing and combination strategies. The absence of severe adverse events suggests that ENB-003 can be safely combined with checkpoint inhibitors and potentially other therapeutic modalities.

Furthermore:

- Only minimal, low-grade adverse events were reported
- No cumulative toxicity signals were observed

Compared to cytotoxic chemotherapy and combination immunotherapy regimens—which are frequently associated with immune-related adverse events (irAEs), organ toxicity, and treatment discontinuation—ENB-003 demonstrates a markedly improved tolerability profile.

From a clinical perspective, this safety profile enables:

- Use in heavily pre-treated and fragile patient populations
- Combination with other therapies without additive toxicity
- Potential for earlier-line use in future studies

8.3 Mechanistic Findings in Phase 1 Biopsies

A tumor biopsy collected 15 weeks post-dosing demonstrated marked increases in tumor-infiltrating T cells, consistent with ENB-003's proposed mechanism of ETBR-mediated endothelial barrier disruption and restoration of immune cell trafficking. Notably, treatment also induced the formation of tertiary lymphoid organs (TLOs) within the tumor microenvironment in preclinical studies- a hallmark of

Table 8.1: Clinical Summary: Efficacy, Safety, and Biomarker Insights

Endpoint	Finding	Clinical Significance
Dose-Limiting Toxicities	None across all 6 cohorts (N=46)	Exceptional safety profile;
ORR in MSS Platinum resistant/ refractory Ovarian Cancer (PROC)	40% objective response rate (N=5)	Vs. <10% historical ORR with Keytruda alone in MSS PROC
DCR in MSS Ovarian Cancer	80% disease control rate (N=5)	Vs. 37% DCR with Keytruda monotherapy (Keynote-100)
DCR in ETBR-Hi patients at 2,000 µg	83% DCR vs. 0% DCR in ETBR-Lo	Validates the companion diagnostic biomarker concept
Durable PFS	20-month PFS in 6th-line platinum-resistant OC patient	Unprecedented durability in otherwise-terminal patients
Durable Response	95% partial response in platinum-refractory, PD-L1 negative OC; 12 month duration	0% historical response to single agent Keytruda
Biomarker Precision	Only ETBR-Hi patients demonstrated tumor shrinkage and survival benefit	Confirms precision patient selection approach

durable antitumor immunity and improved responsiveness to immune checkpoint inhibitors across multiple cancer types (Teillaud et al., 2024; Jiang et al., 2024).

The most notable clinical activity observed in the Phase 1 study occurred in patients with microsatellite-stable (MSS) ovarian cancer, a population traditionally characterized by limited responsiveness to immunotherapy. In combination with pembrolizumab, ENB-003 achieved an objective response rate (ORR) of 40% and a disease control rate (DCR) of 80%, exceeding historical outcomes reported in KEYNOTE-100, where pembrolizumab monotherapy demonstrated an ORR below 10%, a DCR of approximately 37%, and a median progression-free survival of approximately 2.1 months. Collectively, these findings suggest substantial improvement in both tumor response and disease control relative to historical benchmarks.

Responses were also observed in platinum-refractory patients, a subgroup frequently excluded from clinical studies and associated with particularly poor outcomes. These observations support the potential of ENB-003 to provide clinical benefit in patient populations with significant unmet medical need.

ENBOLDEN-101 Phase 1 Biopsy Analyses:

A tumor biopsy obtained approximately 15 weeks after treatment initiation provided direct evidence of biological activity consistent with the proposed mechanism of ENB-003. Key findings included:

- Increased tumor-infiltrating lymphocyte (TIL) density
- Restoration of immune cell trafficking into tumor tissue

These findings provide mechanistic support for ETBR inhibition as a strategy to overcome immune exclusion by promoting immune cell infiltration and re-establishing antitumor immune activity within the tumor microenvironment.

Together, the biopsy and clinical response data provide evidence of target engagement and biological activity in human tumors, supporting further clinical evaluation of ENB-003.

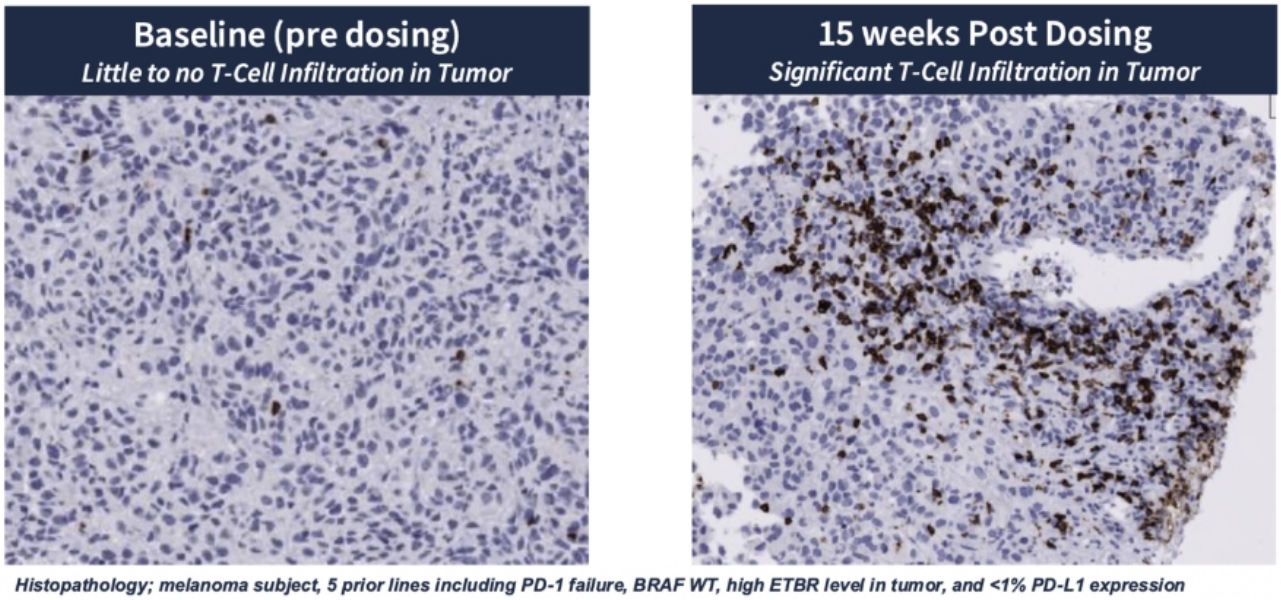


Figure 8.1: Representative tumor biopsy images demonstrating increased intratumoral T-cell infiltration following ENB-003 treatment in a melanoma patient from the Phase 1 study. Baseline (pre-dosing) biopsy showed minimal T-cell infiltration, whereas biopsy specimens obtained 15 weeks after treatment initiation demonstrated substantially increased $CD8^+$ T-cell infiltration within the tumor microenvironment. These findings are consistent with restoration of immune cell trafficking following selective ETBR inhibition.

8.4 Competitive Clinical Performance in Ovarian Cancer

Drug / Regimen	ORR	DCR	mPFS	MSS / Plat-Refractory
ENB-003 + Keytruda (Phase 1, OC)	40%	80%	12 months*	YES — validated in both
Keytruda monotherapy (Keynote-100)	<10%	37%	2.1 months	NO
Liposomal Doxorubicin (SoC)	12%	~40%	2.3 months	N/A
Mirvetuximab (PROC)	24–42%	N/A	5.6 months	NO (excludes plat. refractory)
Bevacizumab (PROC)	21%	N/A	4.7 months	NO (excludes plat. refractory)

**Observed at higher doses in dose escalation study; mPFS will be defined in Phase 2 at recommended Phase 2 dose*

These comparative data are particularly striking because ENB-003 achieved a 40% ORR and 80% DCR in a patient population with a ~8% historical response rate to pembrolizumab (Keytruda) monotherapy. The comparison with currently approved agents — all of which exclude platinum-refractory patients — further highlights the unmet need ENB-003 addresses and the exceptional clinical significance of responses in this patient population.

Beyond response rates,
ENB-003 demonstrated exceptional durability of response, a critical determinant of long-term clinical benefit. Notable outcomes include:

- **20-month progression-free survival (PFS) i**n a sixth-line platinum-resistant ovarian cancer patient
- **12-month durable partial response (~95% tumor reduction)** in a platinum-refractory patient
- These outcomes are particularly striking when compared to standard therapies, where:
- Median PFS typically ranges from **2.1 to 4.7 months**
- Responses are often transient

The observed durability suggests that ENB-003 is not only inducing tumor shrinkage but also **fundamentally altering tumor biology**, consistent with its mechanism of reprogramming the tumor microenvironment.

From a clinical perspective, durable responses in late-line patients are often indicative of:
- Long-term disease control
- Potential survival benefit
- Restoration of effective immune surveillance

8.5 Phase 2 — ENBOLDEN-202: Design and Status

The ENBOLDEN-202 Phase 2
study represents the next stage of clinical development, designed to validate efficacy in larger, biomarker-defined populations.

Key features include:
- Multi-cohort design across ovarian and pancreatic cancers
- Enrollment at leading institutions including MD Anderson Cancer Center
- Biomarker-driven patient selection (ETBR/PD-L1)
- Use of Simon two-stage design for efficiency and early signal detection

The study also includes:
- Combination therapy arms (with Keytruda and Loqtorzi)
- Monotherapy evaluation
- Expansion into pancreatic cancer

The trial is conducted under an open FDA IND (IND #143895), with data readout expected in Q4 2027.

Study Parameter	Detail
Enrollment Status	Phase 2 initiated H2 2025
Study Design	Multi-cohort; Simon 2-stage design for ovarian cancer cohorts
Patient Population	MSS platinum-resistant/refractory ovarian cancer and chemoresistant pancreatic adenocarcinoma
Locations	US and Canada (MD Anderson Cancer Center as lead site)
Regulatory Status	FDA IND open (IND #143895); cleared February 2025
Data Readout	Q4 2027
Pharma Partners	Merck (Keytruda supply) and Coherus (Loqtorzi supply)
Primary Endpoint (OC)	ORR / DoR
Non-Dilutive Funding	~$2M Cancer Research Institute (non-dilutive) + ~$6.25M MD Anderson Cancer Focus Fund (partially dilutive)

8.6 Phase 2 Cohort Structure

Cohort	Treatment	Indication	N (max)
Cohort 1	ENB-003 IV + Loqtorzi	PROC — high grade serous and clear cell	40
Cohort 2	ENB-003 SC + Keytruda	Platinum refractory ovarian cancer	25
Cohort 3	ENB-003 SC + Keytruda	1L/ 2L Platinum resistant ovarian cancer (PROC)	25
Cohort 4	ENB-003 SC Monotherapy	PROC / platinum refractory mix	10
Pancreatic Arm	ENB-003 SC + Loqtorzi	MSS chemoresistant pancreatic adenocarcinoma	Up to 32

The clinical evidence generated to date supports several key conclusions:

- **Proof-of-Concept for ETBR as a Therapeutic Target**: ENB-003 validates ETBR as a clinically actionable mechanism of immunotherapy resistance.
- **Expansion of Immunotherapy to MSS Tumors and PD-L1-Lo Tumors**: ENB-003 enables checkpoint inhibitor efficacy in tumor types historically considered non-responsive.
- **Biomarker-Driven Precision Oncology**: ETBR expression provides a robust framework for patient selection and potential for biomarker-based approval.
- **Potential for Platform-Level Impact**: The mechanism is applicable across multiple tumor types and immune-based therapies, supporting broad clinical expansion.
- **Combination Therapy Backbone**: ENB-003 has the potential to become a foundational therapy used in combination with multiple immunotherapy modalities including anti-PD1/PD-L1, CAR T and cancer vaccines.

Section 9: Published Scientific Evidence and Peer Validation

9.1 Summary of Key Publications

ENB Therapeutics' science has been independently validated through peer-reviewed publications and external recognition from leading oncology research organisations. The following table summarises the key publications and their scientific and clinical significance.

Publication / Source	Key Finding / Significance
Nature Medicine (2008) Buckanovich et al.	Foundational study establishing ETBR as a viable therapeutic target in oncology. **Selective ETBR blockade sensitizes vaccine-resistant ovarian and lung cancer to cancer vaccines in preclinical models.** Demonstrated T-cell homing restoration and ICAM-1 restoration mechanism.
Journal of Experimental Medicine (2024)	**ETBR is the best predictor of non-response to anti-PD1 drugs,** outperforming PD1, PD-L1, and CTLA4. In an analysis of 10,000+ tumors in the TCGA database, ETBR was among the most significant differentially expressed immunomodulators in immunologically quiet tumors.
AACR Annual Meeting, Infante et al. (2014)	**ETBR upregulation drives acquired resistance to BRAF inhibitors.** Roche-Genentech independently validated ETBR as a target by developing an ETBR-targeted ADC that demonstrated clinical activity in drug-resistant melanoma (Phase 1, N=53, 11% partial response).
British Journal of Cancer (2014) Enomoto et al.	ETBR expression in 57% of **oesophageal squamous cell carcinoma cases; high ETBR expression significantly correlated with worse OS and disease-specific survival (p=0.002–0.003);** ETBR correlated with higher microvessel density.
Cancer Research Institute — IPROC Cohort C	ENB-003 selected for the multi-centre CRI IPROC platform study in platinum-resistant ovarian cancer — independent validation by study chairs Drs Odunsi, Zamarin, and MacKay.

Publication / Source	Key Finding / Significance
MD Anderson Cancer Focus Fund	$6.25M commitment validates clinical and scientific rationale, providing financial and institutional endorsement from a leading global cancer centre.
Advanced Therapeutics (Voutouri et al., 2021)	**Demonstrated that endothelin receptor blockade normalises the TME** (reducing stiffness and hypoxia), increases T-cell adhesion to tumor vasculature, and significantly improves immunotherapy efficacy — providing mechanistic support for the ETBR inhibition approach.
PMC11130555 (2024 Review)	**Comprehensive review confirming ETBR's role across multiple TME compartments: endothelial barrier,** CAF-mediated desmoplasia, TAM polarisation, and T-cell exclusion; supports ETBR as a multi-compartmental therapeutic target.

9.2 HITLAB's Evaluation of Clinical Trial Methodology

HITLAB's evaluation indicates that ENB Therapeutics' clinical trials use a robust, multi-endpoint framework, including ORR, DCR, PFS, OS, and companion biomarker analyses, to comprehensively assess efficacy and safety in drug-resistant cancers. This approach aligns with regulatory standards and supports clinically meaningful evidence generation across both disease severity and biomarker-defined outcomes.

The Phase 1 design, open-label, multi-centre, multinational with adaptive dose escalation, aligns with standard first-in-human oncology trials. The Phase 2 ovarian cohorts use a Simon two-stage design, enabling early futility assessment while preserving statistical power.

9.3 Key Differentiators from Existing Therapies

Attribute	ENB-003	Checkpoint Inhibitors	Chemotherapy
Targets ETBR checkpoint	YES — directly	NO	NO
Active in MSS tumors	YES (Phase 1 validated)	Limited / None approved	Partial
Multi-compartment TME action	YES (vessels, cells, stroma)	NO (PD-1 axis only)	NO
Companion diagnostic	In development (ETBR/PD-L1)	Rare	NO
Responses in PD-L1-Low patients	YES (confirmed Phase 1)	Unlikely	N/A
Subcutaneous administration	YES (Phase 2 design)	Mostly IV	Variable
Issued IP through 2039	YES (100% company-owned)	Many with imminent loss of exclusivity	Generic

Section 9.4: Impact, Achievements, Clinical Partnerships, Market Positioning

ENB Therapeutics has generated clinical and translational evidence supporting ETBR inhibition as a novel approach to overcoming immune exclusion in solid tumors. Across Phase 1 studies, ENB-003 demonstrated biological activity in patient populations historically characterized by limited responsiveness to immunotherapy, including microsatellite-stable (MSS) ovarian cancer.

Histopathological analyses demonstrated increased intratumoral T-cell infiltration following treatment, consistent with restoration of immune cell trafficking into the tumor microenvironment. These findings provide mechanistic support for ETBR inhibition as a strategy to address a key barrier to effective antitumor immunity.

Importantly, evidence of biological activity was accompanied by encouraging clinical outcomes. Responses were observed in MSS, PD-L1-low patient populations that have historically derived limited benefit from checkpoint inhibitor therapy. Durable tumor reductions, including near-complete responses maintained beyond 12 months, suggest that selective ETBR inhibition may enhance responsiveness to immunotherapy in immune-excluded tumors.

Collectively, these findings support the continued clinical development of ENB-003 and further evaluation of ETBR as both a therapeutic target and biomarker in immuno-oncology.

Importantly, this impact extends beyond a single indication. Evidence from ovarian, pancreatic, and melanoma models suggests that ETBR inhibition represents a foundational intervention in tumor immunology, with the potential to expand the reach of immunotherapy across a wide range of solid tumors.

ENB Therapeutics has achieved a series of critical milestones across clinical development, scientific validation, and operational execution, positioning the company as a credible and emerging leader in next-generation immuno-oncology.

Clinical Achievements

- Successful completion of the ENBOLDEN-101 Phase 1 trial, enrolling 46 patients across multiple tumor types
- Demonstration of clinically meaningful efficacy signals, including:
- 40% objective response rate (ORR) in MSS ovarian cancer
- 80% disease control rate (DCR)
- Durable responses exceeding 12–20 months in heavily pre-treated patients
- Confirmation of dose-response relationship, with higher efficacy observed at optimized dosing levels
- Establishment of a favorable safety profile, with no dose-limiting toxicities observed

These outcomes are particularly significant given that the treated population consisted largely of checkpoint inhibitor–refractory or historically non-responsive patients, reinforcing the differentiated nature of ENB-003.

Scientific Achievements

- Validation of ETBR as a novel immune checkpoint upstream of PD-1/PD-L1 pathways
- Demonstration of biomarker-driven efficacy, with responses concentrated in ETBR-High / PD-L1–Low populations
- Evidence of tertiary lymphoid organ (TLO) formation, supporting long-term immune activation
- Robust preclinical proof-of-concept across multiple tumor types, including pancreatic and triple-negative breast cancer
- These findings collectively establish ENB-003 as a mechanistically distinct therapy, addressing a root cause of immunotherapy resistance rather than downstream immune activation.

Operational and Financial Achievements

- Advancement from preclinical development through Phase 1 clinical completion with only ~$16M raised, demonstrating exceptional capital efficiency
- Securing $7.5M in Series B commitments and additional non-dilutive funding to support Phase 2 studies
- Establishment of a clear clinical and regulatory roadmap through Phase 2 and potential accelerated approval

This level of execution is notable within the biotech sector, where significantly higher capital is typically required to achieve comparable milestones.

Clinical Partnerships and Institutional Validation

A key pillar of ENB Therapeutics' credibility is its network of strategic clinical and institutional partnerships, which provide both validation and operational leverage.
The company has established clinical trial supply agreements with major pharmaceutical companies, including:

- Merck, providing access to pembrolizumab (Keytruda)
- Coherus, providing access to toripalimab (Loqtorzi)
- These partnerships are highly significant, as they:
- Enable combination therapy development with leading immunotherapies
- Signal external validation of ENB-003's mechanism and potential
- Reduce development risk by leveraging established therapeutic backbones

In addition, ENB Therapeutics collaborates with leading academic and research institutions, including:

- MD Anderson Cancer Center, serving as a key clinical trial site and strategic investor through its Cancer Focus Fund
- Cancer Research Institute (CRI), providing funding and scientific support

Clinical leadership includes globally recognized oncology experts, further strengthening the program's credibility and execution capabilities.

Collectively, these partnerships position ENB Therapeutics within a high-quality clinical ecosystem, enabling efficient trial execution and accelerating development timelines.

Market Positioning: First-in-Class Advantage in a Large, Underserved Market

ENB Therapeutics occupies a distinct and highly defensible position within the oncology landscape, driven by its first-in-class targeting of ETBR and its role in immune exclusion.

First-in-Class Differentiation

ENB-003 is the first selective ETBR inhibitor to enter clinical trials in oncology, providing a clear competitive advantage over:

- Checkpoint inhibitor combinations, which remain ineffective in MSS tumors
- Tumor microenvironment (TME) modulators, which often lack specificity and exhibit toxicity
- Cell therapies, which face scalability and cost challenges

By targeting a previously unaddressed upstream mechanism,
ENB-003 operates in a largely uncontested therapeutic space.

Strong Intellectual Property Position

The company maintains 100% ownership of its intellectual property, with multiple patent families extending protection through 2039 and beyond. This includes:

- Composition of matter patents

- Method-of-use patents across multiple indications
- Combination therapy applications
- This IP position creates a robust barrier to entry, reinforcing long-term competitive advantage.

Large and Underserved Market Opportunity

The market opportunity for ENB-003 is substantial:

- ETBR is expressed in approximately 40% of all solid tumors
- Initial ovarian cancer indication alone represents a $1.5B+ global market
- Broader expansion into pancreatic cancer, melanoma, and other indications significantly increases total addressable market

Importantly, more than 50% of cancer patients do not respond to immunotherapy, representing a large, high-value segment that ENB-003 is uniquely positioned to address.

Platform Positioning

ENB-003 is not positioned as a single-indication drug, but rather as a platform therapy capable of:

- Enhancing multiple immunotherapy modalities
- Expanding across tumor types
- Serving as a backbone for combination regimens

This platform positioning significantly increases both clinical relevance and commercial scalability.

Section 10: Clinical Value Proposition

10.1 For Patients

ENB-003 offers a highly differentiated value proposition for patients with drug-resistant solid tumors, particularly those with microsatellite-stable (MSS) disease who have failed standard therapies and face limited or no remaining treatment options. In these populations, clinical outcomes are typically poor, with low response rates, short progression-free survival, and significant treatment-related toxicity.

The clinical data generated to date demonstrate that ENB-003 has the potential to fundamentally alter this trajectory. In MSS ovarian cancer, a population historically non-responsive to checkpoint inhibitors, ENB-003 in combination with pembrolizumab achieved a 40% objective response rate and 80% disease control rate, compared to <10% response rates with pembrolizumab alone.

Beyond response rates, the durability of these responses is particularly significant. Observations of 12–20 month progression-free survival in heavily pre-treated patients represent a substantial improvement over the typical 2–4 month PFS seen with standard therapies. These outcomes suggest that ENB-003 is not simply inducing transient tumor shrinkage, but rather enabling sustained immune-mediated disease control.

Equally important is the safety and tolerability profile, which directly impacts patient quality of life. Unlike cytotoxic chemotherapy, which is associated with cumulative toxicity, organ damage, and immune suppression, ENB-003 demonstrated:

- No dose-limiting toxicities
- Minimal adverse events

This favorable safety profile allows patients to maintain functional status and avoid the debilitating side effects associated with conventional therapies.

The subcutaneous administration route further enhances patient experience by enabling outpatient treatment and reducing the logistical burden of hospital-based infusions. This is particularly meaningful for patients with advanced disease, where treatment convenience and quality of life are critical considerations.

Finally, the development of an ETBR/PD-L1 companion diagnostic introduces a precision medicine approach that protects patients from ineffective therapy. By identifying those most likely to benefit, ENB-003 minimizes unnecessary exposure to toxicity and maximizes the probability of clinical response.

10.2 For Clinicians

For clinicians, ENB-003 represents a novel therapeutic mechanism that addresses a fundamental limitation of current oncology treatments: the inability of immune cells to access tumor tissue. Most existing immunotherapies operate by enhancing T-cell activity, but their effectiveness is contingent on the presence of T cells within the tumor microenvironment. In immune-excluded tumors, such as MSS ovarian and pancreatic cancers, this prerequisite is not met. ENB-003 directly addresses this gap by restoring T-cell trafficking into tumors through ETBR inhibition, thereby enabling downstream therapies to function effectively.

This mechanism introduces a new category of therapy: an immunotherapy sensitizer, which can be combined with:

- **PD-1/PD-L1 inhibitors (e.g., pembrolizumab, toripalimab)**
- **CAR-T cell therapies**
- **Cancer vaccines**

By acting upstream of these modalities, ENB-003 has the potential to enhance response rates across multiple therapeutic classes, making it highly versatile in clinical practice.
The incorporation of a predictive biomarker (ETBR/PD-L1) further enhances its clinical utility. Unlike many immunotherapies that rely on imperfect biomarkers such as PD-L1 expression alone, ENB-003 enables more precise patient selection, allowing clinicians to tailor treatment decisions based on tumor biology.

Additionally, the favorable safety profile simplifies clinical management:

- Reduced need for intensive monitoring
- Lower risk of severe adverse events
- Greater suitability for frail or heavily pre-treated patients

These attributes collectively position ENB-003 as a clinically practical and scientifically innovative addition to the oncology toolkit.

10.3 For Healthcare Systems and Payers

From a health economics perspective, ENB-003 addresses several critical inefficiencies in current oncology care, particularly those associated with high-cost therapies that deliver limited benefit in large patient populations. Checkpoint inhibitors, while effective in select patients, are associated with substantial costs—often exceeding $200,000 per year per patient—and are frequently administered without reliable predictors of response. This results in significant expenditure on patients who derive little or no clinical benefit.

ENB-003 introduces a cost-efficient alternative through biomarker-guided therapy. The use of an ETBR/PD-L1 companion diagnostic enables:

- Identification of likely responders
- Avoidance of ineffective treatment
- Improved allocation of healthcare resources

In addition, ENB-003's low cost of goods (~$240–$250 per dose) and scalable manufacturing process contrast sharply with the high production costs associated with biologics. This creates the potential for more favorable pricing and reimbursement dynamics.

The durability of response observed with ENB-003 also has important economic implications. By extending progression-free survival and reducing the need for multiple lines of therapy, ENB-003 can:

- Decrease cumulative treatment costs
- Reduce hospitalizations and supportive care requirements
- Improve overall cost-effectiveness

Furthermore, the subcutaneous administration route reduces reliance on infusion centers, lowering infrastructure costs and improving system efficiency. Taken together, these factors position ENB-003 as a therapy that is not only clinically effective but also aligned with value-based healthcare principles, where outcomes are optimized relative to cost.

The market opportunity for ENB-003 is substantial, driven by the high prevalence of ETBR expression across solid tumors and the large proportion of patients who do not respond to existing immunotherapies.

ETBR is expressed in approximately 40% of all solid tumors, encompassing major indications such as ovarian cancer, pancreatic cancer, melanoma, triple-negative breast cancer, and head and neck cancers. This represents a large and under-served patient population with significant unmet medical need.

From a strategic perspective, ENB-003 is positioned as a platform therapy rather than a single-indication drug. Its mechanism of action is applicable across tumor types, enabling:

- Expansion into multiple indications
- Combination with various therapeutic modalities
- Broad clinical adoption

The initial focus on platinum-resistant/refractory ovarian cancer and chemoresistant pancreatic cancer of the MSS phenotype, provides a clear path to market entry, while subsequent expansion into additional indications supports long-term growth.

Financial projections suggest a multi-billion-dollar total addressable market, with potential valuation exceeding $2 billion across indications.
The value proposition of ENB-003 extends beyond its immediate clinical applications, reflecting broader trends in oncology innovation.

As the field moves toward combination therapies and precision medicine, there is increasing recognition that upstream barriers to immune response must be addressed to unlock the full potential of existing treatments. ETBR inhibition represents one such upstream intervention, with the potential to enhance the effectiveness of multiple therapeutic classes. In this context, ENB-003 can be viewed not only as a drug, but as a foundational platform technology that enables:

- Expansion of immunotherapy to previously unresponsive populations
- Development of more effective combination regimens
- Improved patient outcomes at scale

This positioning places ENB-003 at the forefront of next-generation oncology therapeutics, with the potential to deliver both clinical transformation and system-wide impact.

Section 11: Regulatory Strategy and Future Prospects

11.1 Regulatory Pathway

Pathway	Detail
Ovarian Cancer Path	Phase 2 readout Q4 2027; FDA filing and licensing discussions H2 2027; potential accelerated approval for platinum-refractory OC and second-line clear cell OC
Phase 3 Pivotal	250-patient randomised study vs. chemotherapy; potential M&A or Phase 3 initiation H2 2027; Breakthrough Therapy Designation possible after Phase 2
Orphan Drug Designation	Pancreatic cancer and melanoma Orphan Drug Designations already awarded by FDA
Pancreatic Cancer Path	Phase 2 readout following OC data; ENB-003 SC + Loqtorzi in up to 32 MSS chemoresistant PDAC patients; primary endpoint PFS rate at 3 months ≥60%
FDA IND Status	IND #143895; cleared February 2025; open with FDA
Potential Expedited Designations	FDA Fast Track or Breakthrough Therapy Designation following Phase 2 completion

ENB Therapeutics has established a clear and strategically optimized regulatory pathway for ENB-003, designed to accelerate time to market while maximizing clinical and commercial value. The regulatory approach leverages the strength of early clinical data, the severity of the target indications, and the absence of effective therapies in the selected patient populations.
The program is currently operating under an open FDA Investigational New Drug (IND) application (IND #143895), cleared in February 2025, enabling continued clinical development across multiple indications.

The primary regulatory pathway is focused on platinum-resistant and platinum-refractory ovarian cancer, where ENB-003 has already demonstrated compelling Phase 1 efficacy. The ongoing Phase 2 (ENBOLDEN-202) study is designed to support potential accelerated approval, with key endpoints including objective response rate (ORR), duration of response (DoR), and progression-free survival (PFS).

Accelerated approval is particularly feasible in this setting due to:
- High unmet medical need
- Poor outcomes with existing therapies
- Strong early efficacy signals
- Availability of surrogate endpoints (e.g., ORR)

Pending positive Phase 2 results (expected Q4 2026), ENB Therapeutics anticipates:

- **Regulatory submission and FDA engagement in H1 2027**
- Potential approval in platinum-refractory ovarian cancer and second-line clear cell ovarian cancer

In parallel, the company is positioned to pursue Breakthrough Therapy Designation or Fast Track status, which could further accelerate development timelines by enabling:
- Increased FDA interaction
- Rolling review processes
- Priority review timelines

A subsequent Phase 3 randomized trial (~250 patients) is planned to confirm clinical benefit and support full approval. This trial may be initiated independently or in partnership with a larger pharmaceutical company, depending on strategic considerations.

11.2 Pipeline and Expanded Indications

While ovarian cancer represents the initial regulatory focus, the ETBR inhibition platform has broad applicability across multiple tumor types, driven by the widespread expression of ETBR and its role in immune exclusion.

Pancreatic Cancer

Pancreatic cancer represents a key secondary indication, particularly in microsatellite-stable (MSS) chemoresistant pancreatic adenocarcinoma, where treatment options are extremely limited. ENB-003 is being evaluated in combination with immune checkpoint inhibitors, with a

primary endpoint of achieving a **mOS of 8 months**. Given the poor prognosis and lack of effective therapies in this population, pancreatic cancer also presents an opportunity for Orphan Drug Designation, which has already been granted and provides:

- Market exclusivity
- Regulatory incentives
- Reduced development costs

Additional Target Indications

ENB Therapeutics is actively exploring expansion into several high-value oncology indications, including:

- **Triple-Negative Breast Cancer (TNBC):** A subset of TNBC patients exhibit ETBR expression and resistance to checkpoint inhibitors, making them strong candidates for ETBR-targeted therapy.
- **Head and Neck Squamous Cell Carcinoma (HNSCC):** These tumors frequently develop resistance following immunotherapy, creating an opportunity for ENB-003 to restore treatment sensitivity.
- **Metastatic Melanoma (BRAF-mutant):** Independent validation from Roche-Genentech has demonstrated that ETBR contributes to resistance to BRAF inhibitors, providing a strong biological rationale for expansion into this indication.

Next-Generation Pipeline

Beyond ENB-003, the company is developing additional novel ETBR-targeting compounds (ENB-004, ENB-005, ENB-006), which are orally bioavailable small-molecules anticipated to offer:

- Greater convenience
- Broader patient access
- Expanded commercial potential

This pipeline reinforces the positioning of ENB Therapeutics as a **platform compa**ny, rather than a single-asset entity.

11.3 Financing and Exit Strategy

Parameter	Detail
Series B Target	$17.5M total; $7.5M secured; $10M additional required
Cash Runway	Through 2028 with strategic partnerships
Non-Dilutive Funding	$2M Cancer Research Institute (milestone payments) + $6.25M MD Anderson Cancer Focus Fund (partially dilutive)
Exit Strategy	Strategic M&A with Merck, Coherus or large pharma; IPO pathway
Estimated Exit Value (OC only)	$400M–$800M ovarian cancer alone
Estimated Exit Value (full platform)	Potentially >$2B including pancreatic and other indications
ROI Expectations (Series B)	>10X based on comparable oncology deals: Tilos Therapeutics $773M (Merck 2019), iTEOS $625M (GSK 2021), Morphic $3.2B (Eli Lilly 2024)

ENB Therapeutics has established a network of strategic collaborations with leading pharmaceutical and academic institutions, providing both validation and operational support for clinical development.
Key partnerships include:

- Merck (Keytruda supply agreement)
- Coherus (Loqtorzi supply agreement)
- MD Anderson Cancer Center (lead clinical site; $6.25M Cancer Focus Fund investment)
- Cancer Research Institute ($2M in milestone-based funding)

These collaborations serve multiple strategic purposes:

- Enable combination therapy development with established immunotherapies
- Provide access to leading clinical research infrastructure
- Validate the scientific and clinical rationale of the platform

The involvement of MD Anderson and CRI is particularly significant, as both institutions are globally recognized leaders in oncology research and translational medicine.

ENB Therapeutics is currently pursuing a Series B financing round of $17.5 million, of which $7.5 million has already been secured. The remaining $10 million is intended to support:

- Completion of Phase 2 clinical trials
- Expansion into additional indications
- Continued development of the ETBR platform

The company's financing strategy is notable for its capital efficiency, supported by:

- Non-dilutive funding from institutional partners ($7.6M total)
- Low cost of goods for ENB-003
- Scalable manufacturing processes

This approach extends the company's projected cash runway through 2028, enabling it to reach key value inflection points without excessive dilution.
ENB Therapeutics has articulated a clear exit strategy centered on value creation through clinical milestones, with two primary pathways:

1. Strategic Acquisition (M&A)

The most likely exit scenario involves acquisition by a large pharmaceutical company following Phase 2 data readout.
Potential acquirers include:

- Merck (existing partner)
- Coherus
- Other large oncology-focused pharmaceutical companies

This pathway is supported by strong precedent transactions in the oncology space, including:

- Tilos Therapeutics → Merck ($773M)
- iTeos → GSK ($625M)
- Morphic → Eli Lilly ($3.2B)

2. Initial Public Offering (IPO)

Alternatively, ENB Therapeutics may pursue an IPO following Phase 2 validation, leveraging strong clinical data and platform potential to access public markets.

Projected Value Creation

- Estimated valuation for ovarian cancer indication alone: **$400M–$800M**

- Estimated platform valuation across indications: >$2B
- Expected return on investment (Series B): >10x
- These projections reflect:
- Large addressable market
- Strong differentiation
- Platform scalability

The long-term outlook for ENB-003 is shaped by broader trends in oncology, particularly the shift toward:

- Precision medicine and biomarker-driven therapy
- Combination treatment strategies
- Tumor microenvironment targeting

By addressing the upstream mechanism of immune exclusion, ENB-003 has the potential to become
a foundational component of combination regimens, enhancing the efficacy of existing therapies across multiple tumor types.

This positioning is particularly valuable in an oncology landscape where:

- Many therapies fail due to lack of immune infiltration
- Resistance mechanisms remain poorly addressed
- There is increasing demand for scalable, cost-effective treatments

Conclusion

This review highlights the growing clinical and economic burden of drug-resistant solid tumors and the limitations of current immunotherapy approaches in microsatellite-stable (MSS) cancers. A substantial body of preclinical, translational, and clinical evidence supports endothelin B receptor (ETBR) signaling as a key mediator of immune exclusion, limiting T-cell trafficking into tumors and contributing to resistance to checkpoint inhibitor therapy.

ENB-003 is a selective ETBR inhibitor designed to address this upstream mechanism of resistance. Across preclinical and early clinical studies, treatment has been associated with restoration of immune cell infiltration, induction of tertiary lymphoid structures, and encouraging clinical activity in patient populations historically characterized by limited responsiveness to immunotherapy, including MSS and PD-L1-low tumors.

Recent findings identifying ETBR expression as a predictor of anti-PD-1 non-response further support the therapeutic and biomarker potential of this pathway.

The combination of selective ETBR inhibition and biomarker-guided patient selection represents a novel precision-oncology strategy aimed at improving outcomes in immune-excluded tumors.

While additional clinical validation is required, the available evidence supports continued investigation of ENB-003 as a potential approach for overcoming immunotherapy resistance and expanding the benefits of immune-based therapies to patients with significant unmet medical need.

Beyond its clinical rationale, ENB-003 addresses a large patient population with limited treatment options, a biologically validated target, and the potential for biomarker-guided patient selection. Together, these attributes position the ETBR platform as a differentiated approach within the evolving immuno-oncology landscape.

> *"ENB-003 reflects a promising first-in-class approach to dismantling immunotherapy resistance by directly targeting the ETBR checkpoint. By reprogramming the tumor microenvironment to enable immune cell infiltration, ENB Therapeutics demonstrates the potential for durable responses in patients for whom no effective treatment currently exists."*
>
> *Stan Kachnowski, Chair, HITLAB*

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