Zacks Small-Cap Research
Sponsored – Impartial – Comprehensive

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Portage Biotech Inc. (PRTG: NASDAQ)

PRTG: Bridging I-O: Working in Harmony with Checkpoints

Portage's valuation relies on a DCF model and a 15% discount rate applied to our cash flow estimates. Additionally, we apply a success probability of 20% to the adenosine program which recognizes regulatory and commercialization risks. The model includes contributions from the United States and rest-of-world.

Current Price (1/5/2024)	$1.09
Valuation	**$7.00**

INITIATION

Portage is a clinical-stage, oncology-focused biotechnology company targeting adenosine & iNKT pathways in solid tumors. Its pipeline features two platforms: an adenosine antagonist and an iNKT engager. Both are in early-stage clinical trials. Only the adenosine asset is valued in our model.

The adenosine program (PORT-6) seeks to inhibit the A2A receptor subtype. It is the subject of a Phase Ia study & will be evaluated in combination with a checkpoint inhibitor. The iNKT program, designated PORT-2, is the subject of a Phase I/II study as monotherapy and in combination with Keytruda.

The site and setting for PORT-6 & PORT-2 will be defined as they progress through clinical trials. PORT-6 is forecasted to submit a package to regulatory agencies in 2030 followed by approval and first commercialization in 2031.

While initial clinical studies are broadly focused on solid tumors, we expect ultimate focus to be guided by clinical results. Indications most likely to be pursued include prostate, renal cell, colorectal, head and neck, lung, stomach and esophageal cancers. The addressable population may also be biomarker defined.

SUMMARY DATA

52-Week High	**6.46**
52-Week Low	**0.99**
One-Year Return (%)	**-83.8**
Beta	**1.1**
Average Daily Volume (sh)	**35,003**
Shares Outstanding (mil)	**21.0**
Market Capitalization ($mil)	**22.9**
Short Interest Ratio (days)	**0.5**
Institutional Ownership (%)	**11.7**
Insider Ownership (%)	**38.8**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2024 Estimate	**N/A**
P/E using 2025 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of USD)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2023	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2024	$0.0 A	$0.0 A	$0.0 E	$0.0 E	$0.0 E
2025					$0.0 E
2026					$0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2023	-$0.12 A	-$0.06 A	-$0.44 A	-$5.45 A	-$6.49 A
2024	-$0.33 A	-$0.29 A	-$0.28 E	-$0.28 E	-$1.18 E
2025					-$0.86 E
2026					-$0.64 E

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INITIATION

We are initiating coverage of Portage Biotech Inc. (NASDAQ: PRTG) with a target price of $7.00 per share. This value is based on our estimates for a successful development and commercialization of the small molecule A2A receptor antagonist TT-10 or PORT-6 in advanced solid tumors. The candidate is the subject of Phase Ia/Ib trial. Assuming a standard duration of follow-on pivotal studies, PORT-6 is expected to be submitted to regulatory authorities in 2028 in a new drug application (NDA) followed by first sales in 2029. We forecast pivotal studies and commercialization to be initiated with a partner in the United States and around the world. While the iNKT cell engager IMM60 (PORT-2) is also the subject of active studies, Portage is allocating its incremental resources to the PORT-6 and PORT-7 programs.

Portage has demonstrated preclinical efficacy and safety for its A2A and A2B adenosine inhibitors, PORT-6 and PORT-7 along with its invariant natural killer T (iNKT) cell engager, PORT-2. All three are subjects of early-stage trials to further characterize safety, identify the proper Phase II dose and to gain clinical proof of concept for the assets as monotherapy and in combination with a checkpoint inhibitor.

The PORT-6 and PORT-7 adenosine programs are the subject of an adaptive Phase Ia/Ib trial that is identifying the optimal dose for the next stage of development. After identifying a recommended dose, combination safety studies will begin. PORT-6 has begun dosing patients in the Phase Ia portion of its evaluation and is also generating the data to define the recommended Phase II dose. Accrual of Phase I patients is expected to be complete in 1H:24 with further clinical updates provided at scientific conferences in June and November 2024.

The iNKT cell agonist program is differentiated from other immunotherapies by its ability to harness the innate and adaptive immune systems. Portage's asset can stimulate multiple anticancer immune cells, while inhibiting some suppressor cells. Furthermore, iNKT cells have characteristics of both natural killer (NK) and T cells. When iNKT cells are activated, numerous cytokines are released that amplify the innate immune response and activate antigen presenting cells (APCs) and enhance T cell response. Accumulation of adenosine in the tumor microenvironment is immune suppressive and can increase activity of Tregs and myeloid-derived suppressor cells. Blocking the production of adenosine by binding to specific receptors on a variety of immune cells can inhibit tumor growth by limiting angiogenesis and metastatic processes.

Portage is pursuing indications in solid tumors, specifically renal cell cancer (RCC), castrate resistant prostate cancer (CRPC) and non-small cell lung cancer (NSCLC) with its two platforms. Other cancers that may be appropriate for IMM60 and the adenosine antagonist include breast cancer (BC), gastric cancer and melanoma. As the development programs are advanced, we expect to see a narrowing of the focus to the most responsive indications. Solid tumors comprise approximately 90% of all cancers. In the United States, total new cases of cancer are circa two million while around the globe there are about 18 million. Over time, as with other immunotherapies it is reasonable to assume that Portage's candidates will address additional indications if they produce initial clinical success.

While treatments have improved outcomes for many solid tumors, five-year overall survival for some common cancers such as NSCLC range from 23 to 33%, for RCC 77% and for gastric cancer, 33%.[1] While survivability has improved over the last decades, it has been uneven across cancer types. Later stage cancers also demonstrate a much lower rate of survivability, further underlining the unmet need. Approved therapies generally exclude segments of the population with less common tumor profile characteristics. Resistance is another result produced by many therapies, which requires new approaches to overcome.

Emerging approaches, such as adenosine blocking and engaging of iNKT cells may address several of the weaknesses in the approved treatment universe. In particular, reversing the immunosuppressive environment in tumors and unlocking the ability of existing therapies to overcome resistance and extract synergies are primary benefits. For example, iNKT activation can provoke cancer cells to increase the expression of lipid cell surface antigens and immunotherapy targets such as PD-L1 to convert PD-1 negative into PD-1 positive tumors, enabling the body to better recognize and fight cancer. Additionally, Portage's PORT-6 has demonstrated improved potency, selectivity and durability compared with other in-development assets, elevating the company's candidates to a marquee position.

Based on the strong data generated to date, Portage raised $6 million in a registered direct offering finalized after the end of the quarter. This amount builds on the $3.4 million that is on the balance sheet as of September 30,

[1] American Cancer Society datasets.

2023. The company also has access to another $28 million from its agreement with Lincoln Park Capital and $50 million from an at-the-market (ATM) facility with Cantor Fitzgerald. Company management has stated that it has sufficient capital to fund operations until March 2024 prior to accessing the on-demand capital resources. Portage additionally holds shares in public company Intensity Therapeutics (NASDAQ: INTS) which were recently valued at $5.6 million. The securities are available for sale.

The ongoing Phase Ia/Ib trial in PORT-6 should report interim data by mid-2024 and start the Phase Ib portion of the study in 2H:24. PORT-7 is slated to begin a Phase Ia in 1H:24. Further refinement of indication and setting is expected to be complete after the Phase II trial and implemented in a subsequent pivotal trial in 2026. Based on this timeline, we anticipate a new drug application (NDA) for PORT-6 by 2028 and first sales in 2029.

Key reasons to own Portage shares:

- **Experienced pharmaceutical management team with development & commercialization successes**
  - **Bristol Myers Squibb, Johnson & Johnson,**
  - **Strong academic & industry network**
  - **Team members have obtained approval for multiple assets**
- **Product focus on candidates that address known resistance in approved therapies**
- **Two platforms with multiple clinical studies underway**
  - **Anti-adenosine platform featuring PORT-6 (TT-10) and PORT-7 (TT-4)**
    - **Targets A2A & A2B expressing solid tumors alone and with Keytruda**
    - **Reverses immunosuppressive tumor microenvironment**
    - **No dose limiting toxicities observed**
    - **May seek approval in biomarker defined population**
  - **iNKT engager (PORT-2)**
    - **Offers features of both natural killer and T cells**
    - **Stimulates innate and adaptive immune system for anti-cancer response**
    - **Evaluated alone and in combination with Keytruda**
- **Offers additional assets on featured platforms**
  - **PORT-3 – includes combination of PORT-2 with vaccine**
  - **A2A/A2B dual antagonist**
  - **Gut-restricted A2B antagonist**

In the following sections we describe immunotherapy, immuno-oncology (I-O), checkpoint inhibitors (CIs) and the evolution of agents to Portage's library of offerings. We review the mechanism of action of the adenosine antagonist and the iNKT inhibitor as well as discuss the preclinical support for advancing both assets into the clinic. We follow with a description of the ongoing Phase I/II trials, providing a timeline for expected milestones. Portage is targeting solid tumor malignancies in both of its active programs. Primary indications being pursued are expected to be RCC, CRPC, breast cancer (BC), NSCLC and gastric cancer all with high A2A expression. We discuss other competitors in the immuno-oncology space, including several peers advancing adenosine and iNKT programs. The subsequent section reviews recent financial and operational history for the company followed by an introduction to the management team and a summary of Portage-specific risks. Our valuation discussion details the assumptions used to determine our target price. We expect first sales in 2031 for PORT-6 after favorable trial outcomes, successful NDA submission and FDA approval. Our work generates a target price of $7.00 per share for Portage Biotech, Inc.

Immunotherapy

Immuno-oncology

Immuno-oncology (I-O), or cancer immunotherapy, is an approach to fighting cancer that leverages the body's immune system to attack the disease. Normally, the body's immune system can eliminate cancer cells, but in some cases, these mutant cells can adapt to hide by expressing deterrent proteins on their surface among other mechanisms. When I-O drugs or biologics are administered, they allow the immune system to recognize harmful cells and destroy them, in many cases with fewer, short-lived side effects compared to surgery, chemotherapy and radiotherapy. Immunotherapy is preferred because it is frequently associated with fewer adverse events, maintains its potency, works well in conjunction with other therapies and is able to better target the malignancy. Several classes of immunotherapy exist including therapeutic vaccines, checkpoint inhibitors, immune modulators, adoptive cell therapy (CAR-T), oncolytic viruses and antibody drug conjugates to name the most prominent examples. I-O can be either active or passive. Active approaches direct the immune system to kill cancer cells by targeting tumor antigens. Passive approaches augment existing tumor responses by the use of a variety of proteins, lymphocytes and cytokines to enhance their activity.

Checkpoint inhibitors (CIs) have become one of the most visible immunotherapies in life sciences. Initial work in the early 1980s by industry luminary James Allison tested checkpoint inhibitors in animal models. The first immune checkpoint molecule was discovered in 1987, designated cytotoxic T-lymphocyte antigen number 4 (CTLA-4). Further work led to the start of the first trial for the drug class in 2000 with ipilimumab, a monoclonal antibody that binds and blocks the CTLA-4 receptor. This shift to immunotherapy advanced medicines based on the tumor makeup rather than the site of the disease. After a decade of clinical trials and traversing the regulatory process, ipilimumab was approved in 2011.

While the potential of checkpoint inhibitors has been long understood in the oncology field, it became more widely known to the general public when Jimmy Carter announced he was cancer free in 2015. The former president's metastatic melanoma was treated with the investigational drug pembrolizumab, a different type of checkpoint inhibitor targeting the programmed cell death protein 1 (PD-1). The monoclonal antibody (which is the form of most checkpoint inhibitors) was able to release the brakes on his immune system, thereby allowing it to attack and shrink his tumors. The medicine allowed President Carter to return to health without the need for further treatment. This triumph put checkpoint inhibitors on the front page for not only those in the oncology field but also for the layman.

While CIs were an impressive breakthrough in immuno-oncology, there are shortcomings. Complete responses are frequently below 10% and most patients generate no response or a partial response. CIs work well in highly immunogenic indications, but are less effective in common cancers such as breast cancer, non-small cell lung cancer (NSCLC), prostate cancer and colorectal cancer. One of the reasons why approved therapies in the anti-PD-1, PD-L1 and CTLA-4 classes fail to stimulate clearance of the tumor is the lack of tumor-infiltrating lymphocytes (TILs) in and around the tumor. This condition is known as a cold or immunologically suppressed tumor.

CI's allow the immune system's fighters to engage. However, the immune cells need to infiltrate the tumor microenvironment for the immunotherapy to work. Resistance mechanisms may emerge, where cancer cells may upregulate other immune checkpoints or recruit immunosuppressive cells, such as regulatory T cells or myeloid-derived suppressor cells, to counteract the immune response induced by the checkpoint inhibitors. This has led researchers to identify combination therapies that can activate the immune system in the tumor environment, allow it to enter and help overcome resistance mechanisms. iNKT agonism and adenosine blocking have both shown synergies with CIs in both preclinical and clinical studies.

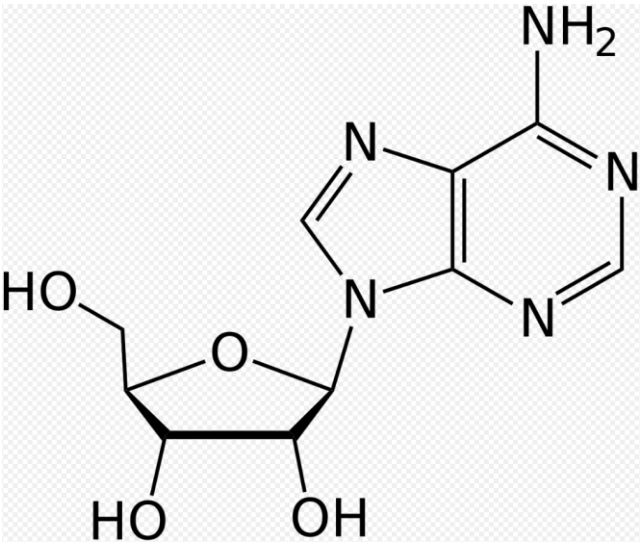
Checkpoint inhibitors have produced substantial benefits to patients providing impressive remission rates in numerous cancers including melanoma and NSCLC. However, resistance has emerged as a new barrier to treatment and researchers are seeking ways to overcome it through combination therapies. Some of the hurdles that have materialized include cold tumors that lack T cell infiltration, low immunogenicity and immune recognition and a suppressive tumor environment.

CIs largely use the same mechanism of action. Other complementary approaches are needed to overcome the limitations of this immunotherapy and overcome resistance. Checkpoints have been approved for use with chemotherapy and are being investigated with other therapies including epidermal growth factor receptor (EGFR) inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, cancer vaccines, antibody drug conjugates and others. Some less common but compelling alternative combinations may include adenosine blocking and iNKT agonists which may address some of the blind spots in CI therapy.

Adenosine Receptor Modulation

Adenosine is a building block of RNA and DNA along with guanosine, cytidine and thymidine. It forms the adenine nucleotide base in these nucleic acids. The molecule consists of an adenine attached to a ribose via a β-N9-glycosidic bond. Adenosine also acts as a signaling molecule by activating adenosine receptors. It can play a role in a variety of physiological processes including sleep, vasodilation and neuroprotection. Among other functions, adenosine has an important regulatory role in the immune system. When adenosine binds to the various adenosine receptors, it can inhibit the activity of the immune system. This is done by suppressing the release of pro-inflammatory cytokines, T cell activation and natural killer cell activation.

Exhibit I – Molecular Structure of Adenosine[2]



While adenosine receptor binding prevents overactivation of the immune system and excessive inflammation, it may also allow cancers to proliferate unchecked. This can occur through suppression of the antitumor immune response, suppressing the activity of T cells and macrophages. It can also allow cancer cells to evade the immune system and spread. Adenosine can also promote tumor angiogenesis when it binds to adenosine receptors on endothelial cells which can provide cancer cells with necessary oxygen and nutrients. The presence of the molecule can also stimulate cancer cells to invade surrounding tissue and metastasize to other parts of the body.

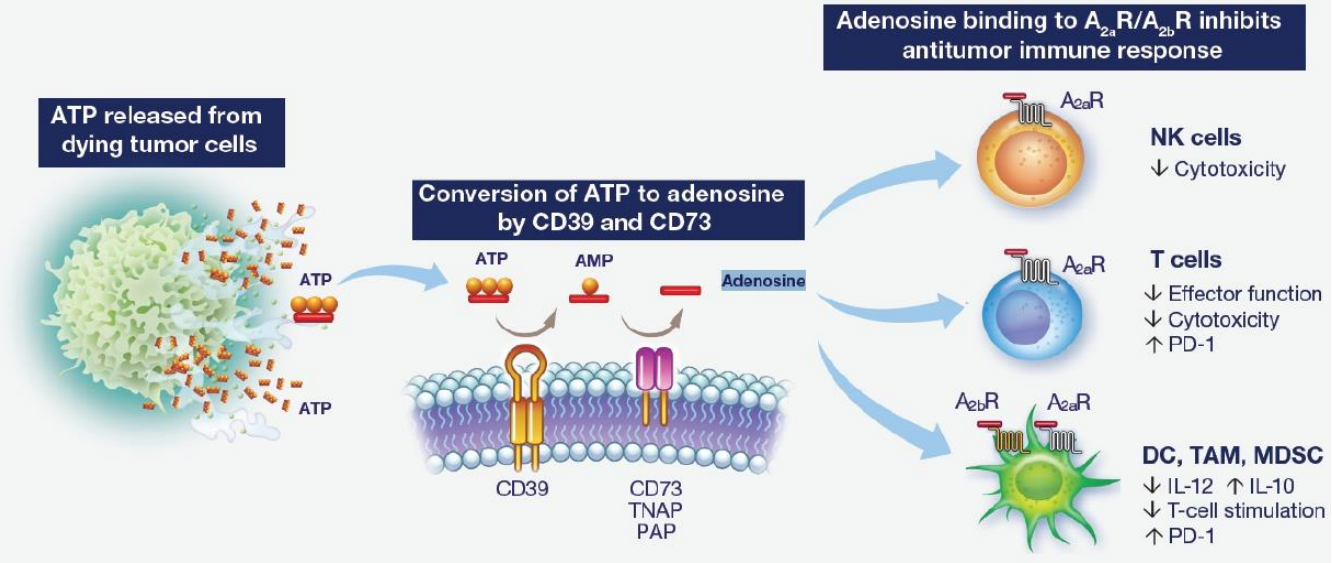
As adenosine plays a critical role in tumor immunity, angiogenesis and metastasis, therapies have emerged to address its role including the development of adenosine receptor antagonists, adenosine-degrading enzymes and agents that obstruct adenosine production. Some of the most prominent non-selective adenosine antagonists include caffeine and theophylline. One approved example is istradefylline, an A2A-specific antagonist used in Japan for treating Parkinson's disease.

Adenosine receptors appear on a variety of cell types including neurons, cardiomyocytes, vascular endothelial, immune, liver and kidney cells among others. Adenosine receptors consist of a group of G protein-coupled receptors that mediate the physiological actions of adenosine. There are four types of receptors including A1, A2A, A2B, and A3. The A2A and A2B receptors activate adenylate cyclase, regulating cyclic AMP synthesis. Adenosine receptors appear throughout the body and function as part of the adenosine signaling system. The system helps regulate neurotransmission, cardiovascular function and anti-inflammatory responses. In this report, two receptors in particular are of importance: A2A and A2B.

Other derivatives of adenosine include the energy carriers adenosine mono- (A**M**P), di- (A**D**P), and triphosphate (A**T**P). The breakdown of ATP to ADP or AMP powers most forms of biological work. Adenosine can accumulate via the dephosphorylation of AMP and is also produced by inflammatory cells, including mast cells, leucocytes, neutrophils and eosinophils. As the various intermediates and metabolites convert to adenosine, it binds to the adenosine receptors producing an antitumor immune response. Some of the cells most significantly affected include natural killer cells, T cells, dendritic cells, tumor associated macrophages and myeloid derived suppressor cells.

[2] Adenosine, NEUROtiker, Public domain, via Wikimedia Commons.

Exhibit II – Adenosine's Contribution to the Immunosuppressive Tumor Microenvironment[3]



Cellular signaling by adenosine occurs through four known adenosine receptor subtypes which include A1, A2A, A2B, and A3. A1, and A2A have a high affinity for adenosine while A2B, and A3 have a relatively lower affinity. Members of this receptor family have similar architectures with a seven transmembrane α-helical structure. All adenosine receptors are coupled to the G-protein. Adenosine A1 and A3 receptors are coupled to the inhibitory G-protein and adenosine A2A and A2B receptors are coupled to the stimulatory G-protein.

Adenosine is responsible for many critical functions including neurotransmitter release, synaptic plasticity and neuroprotection in ischemic, hypoxic and oxidative stress events. It also affects vascular dilation or constriction of blood vessels, inhibits lipolysis and stimulates bronchoconstriction. Activated A2A receptors can exert immunosuppressive effects through neutralization of T cells and natural killer cells, allowing tumors to grow unchecked. It may also contribute to angiogenesis which can supply nutrients to the tumor. By blocking the receptor, immune activity may be restored allowing the immune system to clear the cancer. The molecule further regulates T cell proliferation and cytokine production. Adenosine binding to A2A is anti-inflammatory and downregulates a variety of inflammatory proteins.

Hypoxia is a common feature of the tumor microenvironment that promotes immunosuppression and stimulates the increased production of adenosine. Hypoxia can promote tumor survival, increase resistance to treatment and induce angiogenesis. Hypoxia inhibits oxidative phosphorylation in mitochondria, leading to an increase in the AMP to ATP ratio and activating the CD73 enzyme which converts AMP to adenosine. At the same time, adenosine, whose levels became elevated during hypoxia, further enhances angiogenesis by stimulating A2B receptors. This creates a positive feedback loop of hypoxia, adenosine and vascular endothelial growth factor (VEGF).[4] In other words, hypoxia regulates the levels of adenosine by inhibiting enzymes involved in the destruction of adenosine and simultaneously increasing the activity of enzymes that generate it. Furthermore, adenosine signaling impairs immune cell function. Through the A2A adenosine receptor on immune cells like T cells and natural killer cells, adenosine inhibits its antitumor immune responses. This allows cancer cells to multiply, consume more oxygen and reinforce the cycle.

[3] Portage KOL Event Presentation Slide Deck, March 2023.
[4] VEGF is a protein that stimulates the formation of new blood vessels.

Invariant Natural Killer T (iNKT) Cells

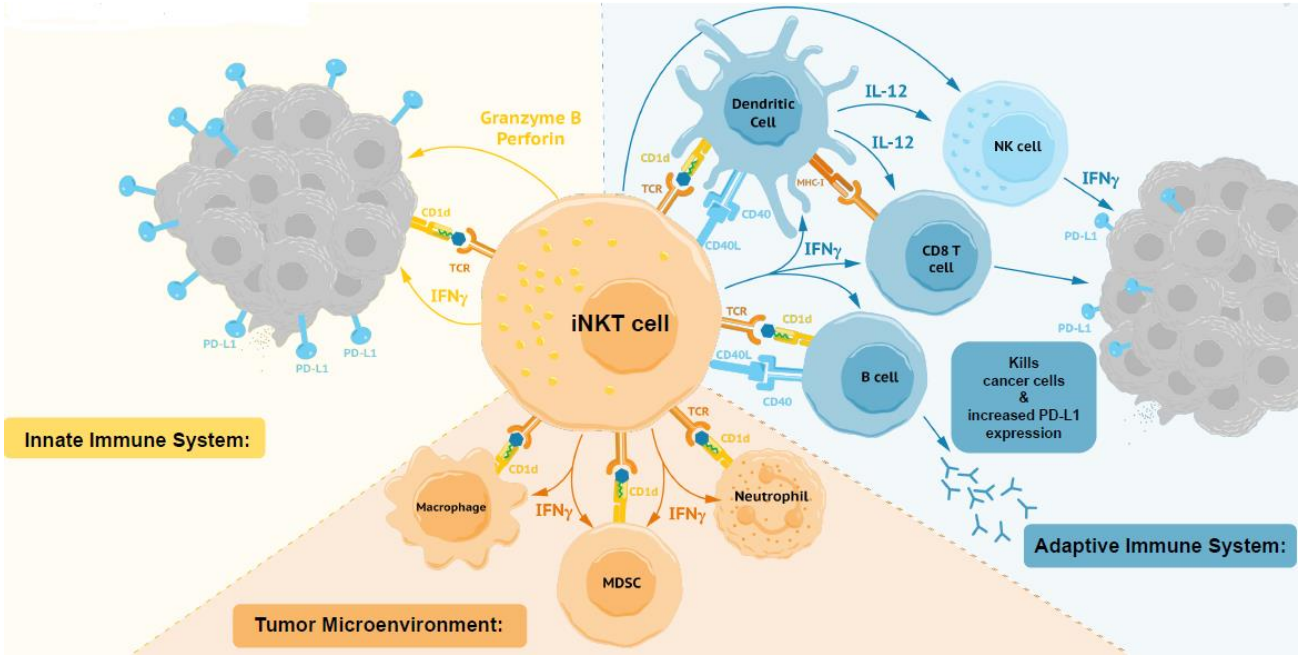
Invariant natural killer T cells (iNKTs) are a specific population of T cells that express an invariant T cell receptor and react to lipid-based antigens complexed with CD1d.[5] CD1d plays an important role in the immune response to cancer and infections and is involved in the regulation of autoimmunity. iNKTs have characteristics of both T cells and natural killer (NK) cells and exhibit behaviors of both adaptive and innate immune responses.

Innate functions of the iNKT cell include rapid response to infection and cancer, antimicrobial defense and tumor surveillance. Adaptive functions include regulation of the immune response, activation of dendritic cells and modulation of autoimmunity by suppressing the activation of T cells and B cells. iNKT cells play an important role in anti-tumor immune responses and are a distinct class of T lymphocyte displaying a limited diversity of T-cell receptors. They recognize lipid antigens on the surface of tumor cells and produce a cytokine response within hours of stimulation without the need for clonal expansion. iNKT cells activate multiple immune system components, including dendritic cells, T-cells and B-cells and stimulate an antigen-specific expansion of these cells.

iNKT cells are relatively rare in circulating blood and liver, comprising 1% or less of total T cells. The cells are most commonly found in the blood, liver, bone marrow, spleen and lungs. Frequency is highest in human adipose tissue, with their prevalence rising to 10-25%. Despite the low prevalence in most tissues, the cells can be rapidly activated, provoking an immune response. iNKT cells express an invariant T cell receptor alpha chain that specifically recognizes glycolipid antigens presented by the MHC class I-like molecule CD1d. This gives them a limited specificity for lipids and glycolipids.

In contrast to conventional T cells which respond to peptide antigens, iNKTs respond to and are activated by glycolipid antigens. *In vitro* studies frequently activate iNKT cells with α-galactosylceramide (α-GalCer)[6] which has strong anti-tumor activity. When the lipid antigen is presented by the major histocompatibility complex (MHC) class Ib molecule CD1d, iNKTs secrete cytokines, beginning an immune response. The type of lipid antigen presented will determine the cytokine released ranging from TNF-α to IFN-γ, IL-2 and IL-4 among others. The CD1d restriction identifies and defines iNKT cells from other T cell populations.

Exhibit III – iNKT Cell Relationship with Immune System and Tumor Microenvironment[7]



[5] CD1d is a glycoprotein found in humans that belongs to the CD1 family of molecules. These molecules are part of the major histocompatibility complex (MHC) class I-like family, primarily known for their role in presenting lipid antigens to NKT cells.
[6] α-GalCer is derived from agelasphins, which are naturally occurring glycolipids that were isolated from the marine sponge *Agelas mauritianus*.
[7] Portage corporate presentation December 2023.

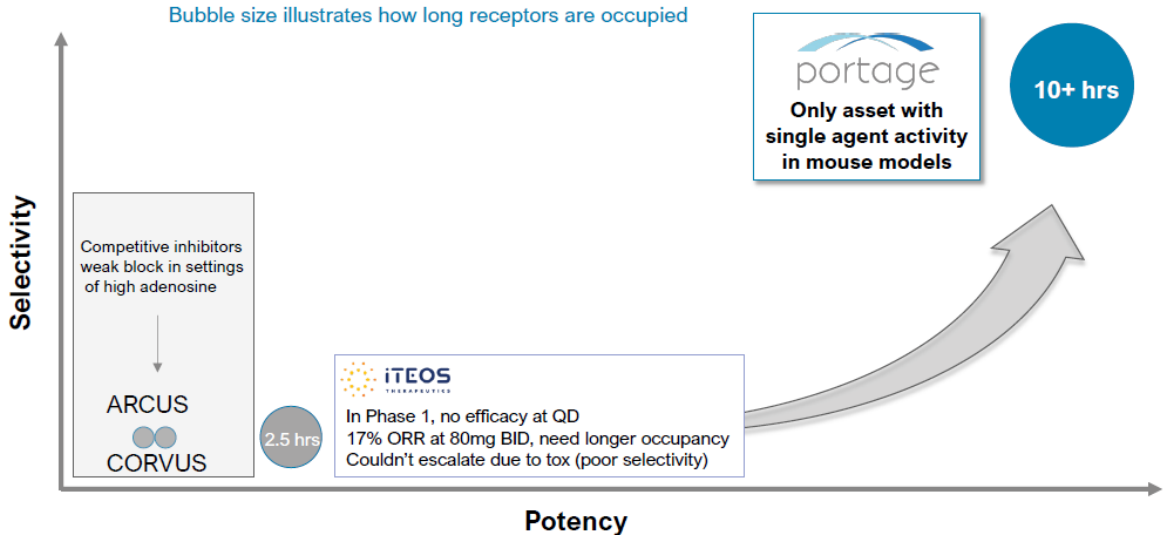
Therapeutic Platforms

PORT-6 (TT-10) and PORT-7 (TT-4): A2A and A2B Antagonists

Portage offers several adenosine receptor antagonists in its pipeline including those targeting the A2A and A2B receptors. The company is focused on developing both its A2A and A2B receptor antagonists which bind to their respective receptors. The candidates, which are designated PORT-6 (TT-10) and PORT-7 (TT-4), exhibit high-affinity receptor binding. PORT-6 in particular has a dissociation rate half-life of over ten hours and is only slowly displaced from its receptor even in the presence of super-physiologic concentrations of adenosine.

In contrast to other adenosine receptor antagonists, PORT-6 offers improved durability, potency and selectivity which may address some of the shortcomings faced by other candidates in the class. PORT-6 binds to receptors for over 10 hours in preclinical models, in comparison with other agents that bind for less than half this duration. These binding kinetics allow for less frequent dosing. Potency is an important attribute as it allows PORT-6 to out-compete the natural ligand, increasing its effectiveness when there are high levels of adenosine in the tumor microenvironment. PORT-6 selectivity is another strong point which allows it to bind only to the A2A receptor thereby avoiding off-target effects and allowing for higher dosing and associated greater efficacy.

Exhibit IV – Relative Profiles of A2A Antagonists Based on Public Data[8]



Cancers with high levels of adenosine A2A receptor expression include prostate, non-small cell lung, head and neck and renal cell cancer. A2B receptor expression is additionally found in relatively higher levels in colorectal, endometrial and ovarian cancer. Portage has launched a basket trial that will examine several cancers that demonstrate a high proportion of adenosine and expression of adenosine receptors.

Portage intends to develop a companion diagnostic to identify a biomarker defined patient population. Several gene marker biomarker signatures have been evaluated and peers using a biomarker defined population have shown improved survival in patients administered the A2A antagonist with high adenosine expression. Portage appears to favor using an immunohistochemistry (IHC) derived biomarker to select high adenosine expressing patients. Ultimately, similar to other I-O drugs that have been approved for MSI-high or mismatch repair deficient tumors, PORT-6 may be approved based on the biomarker profile of the tumor rather than its origin site.

ADPORT-601: TT-10 (PORT-6) and TT-4 (PORT-7): Phase I Study

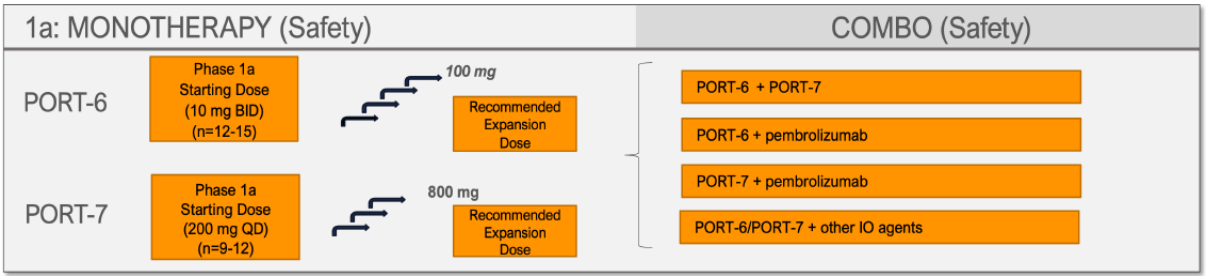
Portage's Phase Ia/Ib trial evaluating TT-10 (PORT-6) and TT-4 (PORT-7) is designated ADPORT-601. It will identify subjects with high A2A and A2B receptor expression using an immunohistochemistry-based assay. Details of the first in human study of TT-10 as a single agent in subjects with advanced selected solid tumors are listed on clinicaltrials.gov under the identifier NCT04969315. It is a basket trial primarily evaluating renal cell, non-small cell lung and castrate resistant prostate cancer. The study will be conducted in two phases. The first phase, dose escalation, will determine the maximum tolerated dose (MTD) or recommended Phase II dose, safety and tolerability of TT-10

[8] Portage KOL Event Presentation Slide Deck, March 2023.

in subjects with advanced stage cancer who have failed or are not eligible for standard of care treatment. The second phase, dose expansion, will be to further explore the safety and tolerability of the MTD and/or Phase II dose and measure pharmacokinetics, pharmacodynamics, anti-tumor activity and efficacy of TT-10. Eight sites around the United States have been secured to run the trial.

The primary endpoint is safety with a secondary objective of identifying a recommended dose for efficacy studies. Portage is expected to pursue PORT-6 and PORT-7 in monotherapy and in combination with Keytruda.

Exhibit V – ADPORT-601 Study Design[9]



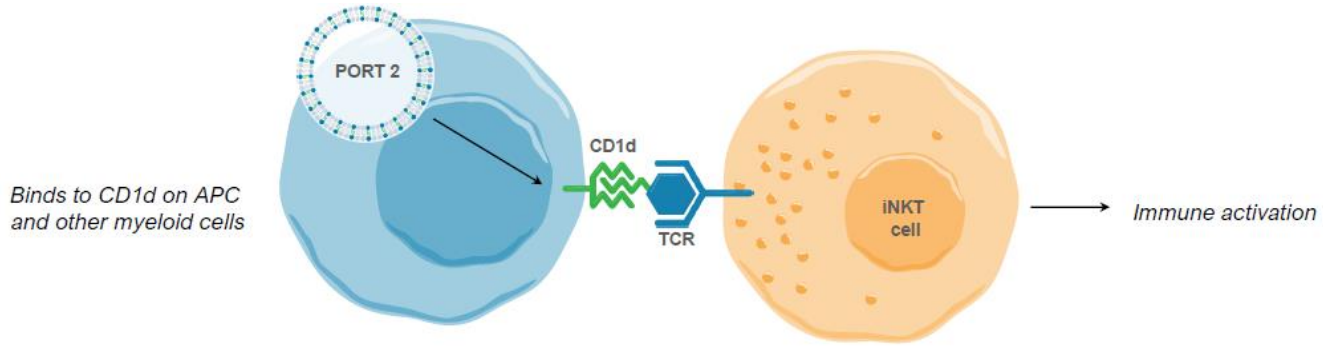
A poster was presented at the Society for Immunotherapy of Cancer (SITC) in early November 2023, updating stakeholders on the trial status. The first patient, first visit was completed in June 2023 and enrollment is ongoing. Four patients have been treated and the second dose cohort is open for enrollment. Data from the studies will contribute to further research on the adenosine pathway. Optimizing inhibition of the adenosine receptors will help identify the contribution of the adenosine signaling pathway in suppressing anti-tumor activity using multi-omic analyses.

IMM60 (PORT-2): iNKT Cell Agonist

While checkpoint inhibitors and other immunotherapies have improved the survival and side effect profile of cancer treatment and provided a complement and even an alternative to surgery, radiation and chemotherapy, there is still much to do. This unmet need has encouraged new candidates to emerge that seek to precisely stimulate the immune system and work in conjunction with other immunotherapies. In response, Portage has been developing PORT-2, an optimized synthetic iNKT agonist that demonstrated strong binding affinity to a human iNKT-cell T cell receptor in preclinical studies. The agent is a lipid composed of a threitol sphingoid base linked to a fatty acid using an amide bond.

Threitol-ceramide, or IMM60, binds to the CD1d molecule that appears on the surface of iNKT cells. Similar to the effects of α-GalCer, this binding activates the iNKT cell, delivers an antigen and stimulates the release of cytokines and perforin[10] in the presence of cancer cells. Once the connection has been made between IMM60 and the iNKT cell, the latter begins to produce cytokines and exert cytotoxic effects against tumor cells. iNKT cells can also influence angiogenesis, which can contribute to cancer cell growth.[11]

Exhibit VI – iNKT Engager (PORT-2), A Liposomal Formulation of IMM60[12]



[9] Portage Poster, presented at SITC 2023. ADPORT-601 (TT-10-101): First-in-Human Study of Adenosine 2A (A2A) and Adenosine 2B (A2B) receptor antagonists in Participants with Selected Advanced Solid Tumors.
[10] Perforin is a pore-forming protein that is released by cytotoxic T lymphocytes and natural killer cells. It plays a critical role in the immune system's response to viruses, bacteria, and cancer cells. Perforin molecules insert themselves into the membranes of target cells, creating pores that allow granzymes and other cytotoxic molecules to enter the cell and induce apoptosis.
[11] Kyriakakis, E., *et al*. IL-8-mediated angiogenic responses of endothelial cells to lipid antigen activation of iNKT cells depend on EGFR transactivation. Journal of Leukocyte Biology. July 2011.
[12] Portage corporate presentation December 2023.

The composition of IMM60 solves several challenges that arise with stimulation of iNKT cells using α-GalCer. α-GalCer is composed of glycosides that can be unstable and it presents an inferior liposomal formulation. It binds weakly to T cell receptors and offers modest bioavailability. Repeated use of α-GalCer can lead to induced anergy or long-term unresponsiveness of iNKT cells. The structure of IMM60 addresses these shortcomings through better design which improves durability, stability, binding affinity, bioavailability and response.

Exhibit VII – IMM60 Molecular Structure[13]



IMM60 is an invariant natural killer T (iNKT) cell agonist that affects multiple components of the immune system. IMM60 upregulates PD-L1 expression, allowing anti-PD-1 therapies to work. The compound also activates antigen-progenitor cells and CD8+ T cells, which regulate anti-tumor responses. IMM60 can potentially overcome resistance mechanisms that arise from the use of existing therapies.

IMM60 (PORT-2): Phase I Study

Details of the PORT-2 clinical trial were included in the International Standard Randomised Controlled Trial Number (ISRCTN) registry under the identifier ISRCTN80472712 and also under clinicaltrials.gov study record number NCT05709821. The records provide additional details of the Phase I/II trial design including total estimated enrollment of 100 subjects and site locations in the US, Spain and United Kingdom. Enrolled patients will be adults with histologically confirmed diagnosis of stage IV NSCLC and a PD-L1 assessment.

Portage ran a Phase I study to evaluate the safety of IMM60 and determine dose limiting toxicities. Initial work began with monotherapy in a 3x3 design at 1 mg, 3 mg and 9 mg/m^2 administered intravenously every three weeks for six cycles. IMM60 was also evaluated in combination with pembrolizumab at 3 and 9 mg/m^2. Biopsies and blood were taken from enrolled patients to evaluate progress and biomarkers before and during treatment. All enrollees had been pretreated with checkpoint inhibitors.

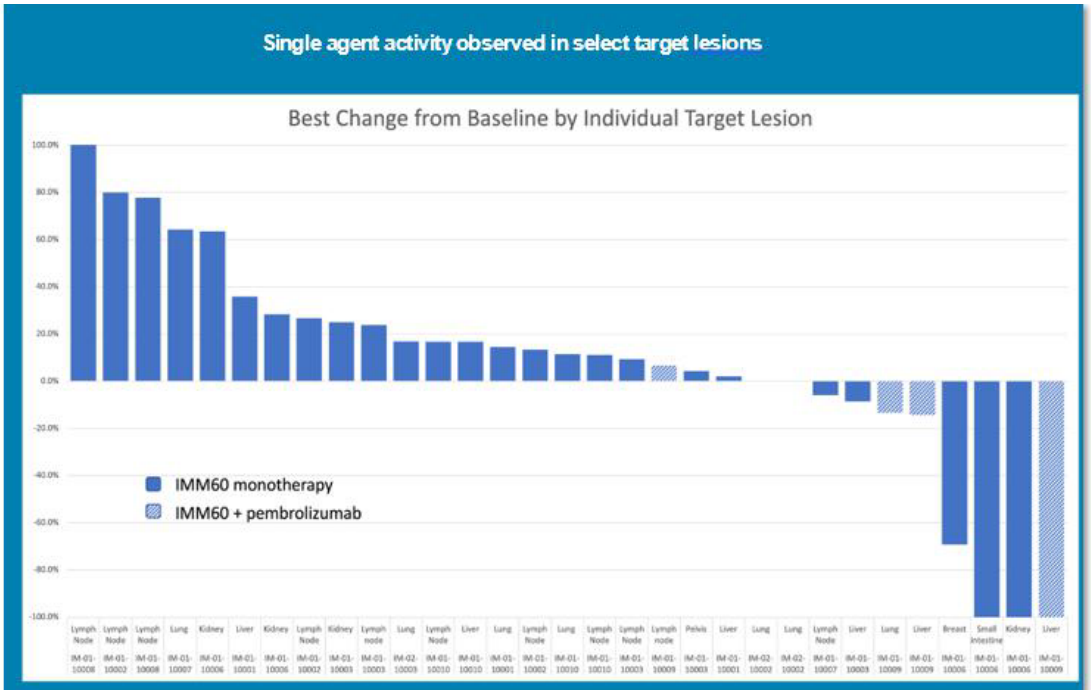
By November 2023, 65 infusions had been administered to 15 subjects which produced no serious adverse events or dose limiting toxicities. Adverse events were mild with only Grade 1 or 2 incidents reported in the following categories: pain, fatigue, edema, dizziness, weight loss, nausea, vomiting, itching, weakness, pleural effusion, hypertension, AST/ALT elevation and hair loss. The study concluded that IMM60 was well tolerated at 1, 3 and 9 mg/m^2. Two patients were treated with IMM60 and pembrolizumab with no unexpected toxicity. A higher fixed dose of 36 mg/m^2 will be tested based on the favorable safety profile. When the recommended Phase II dose is identified, it will provide the foundation for starting a Phase II study.

Pharmacodynamic measurements support activation of iNKT, dendritic, and NK cells and there was evidence of single agent activity. Pharmacokinetic results demonstrate dose proportionality. Dosing has begun for the combination portion of the Phase I in parallel with the dose finding study. The goals for the study are to evaluate IMM60 in combination with an anti-PD1 antibody.

Clinical activity in this group included one patient at the 3 mg/m^2 dose who achieved a >50% reduction in a 4 cm mediastinal lesion and resolution of 2.2 cm lesion in the small bowel mesentery as well as multiple pathologic lymph nodes. The RECIST best response was stable disease.

[13] Portage corporate presentation December 2023.

Exhibit VIII – Target Lesion Response (IMM60)[14]



Safety results for IMM60 monotherapy identified no dose limiting toxicities, no serious adverse events or adverse events of Grade 3 or above in 14 patients. Two Grade 2 adverse events were observed including fatigue and hypertension. The most common Grade 1 events were two patients (14%) reporting dizziness and two patients (14%) producing AST/ALT elevation. The two patients that were treated with IMM60 and pembrolizumab experienced only low-grade adverse events consistent with the safety profile of pembrolizumab.

PORT-3

PORT-3 combines IMM60 with a vaccine. It is a nanoparticle co-formulation of the iNKT engager IMM60 and NY-ESO-1 immunogenic peptides developed for the treatment of NY-ESO-1 positive solid tumors. The combination is being investigated in the PRECIOUS Phase I trial, which dosed its first patient in April 2021. Portage is not involved in administering or financing the trial and it is an investigator sponsored study. Academic partner Radboud University Medical Center and the EU Horizon 2020 Program manage, run and fund the study. While the pace has been slow, the trial has continued with additional grant funding. PORT-3 is a platform that can potentially be combined with a variety of companion vaccines and antigens.

Data has shown that coformulation of an iNKT agonist with tumor-specific antigens results in a substantial improvement in efficacy compared to administering the treatments separately. Published data with PORT-3 constructs show superior monotherapy activity compared to PD-1 in melanoma and head and neck cancer models, with added benefits when PORT-3 is combined with a checkpoint inhibitor. We expect to see a slow advance of this trial due to limited funding.

[14] Portage 6-K filing, November 28, 2023.

Portage Pipeline

Portage features multiple assets in its pipeline with several of these programs active under the Portage umbrella: PORT-6, PORT-7 and PORT-2. Other programs, such as PORT-3 are being run by collaborators or are paused. We anticipate that following the January 4th, 2024 press release announcing the narrowing of the company's focus to PORT-6 and PORT-7, that PORT-2 will not advance further unless new capital or partner resources are secured.

Exhibit IX – Portage Pipeline[15]

Adenosine Platform

ASSET	INDICATION	STAGE	# of PTS	Interim Data	Final Data
PORT-6 (A2A)	A2A exp Solid Tumors	Phase 1a	21-27	ASCO 2024	SITC 2024
PORT-7 (A2B)	A2B exp Solid Tumors	Phase 1a*	18	SITC 2024	ASCO 2025
PORT-6 (A2A)	A2B exp Solid Tumors	Phase 1b*	20	SITC 2024	SITC 2025
PORT-7 (A2B)	A2A exp Solid Tumors	Phase 1b*	20	SITC 2025	ASCO 2026
PORT-6 (A2A) + CPI	A2A exp Solid Tumors	Phase 1b*	20	SITC 2024	SITC 2025
PORT-7 (A2B) + CPI	A2B exp Solid Tumors	Phase 1b*	20	SITC 2025	ASCO 2026
PORT 6/7 (A2A/2B) +CPI	BM enriched	Phase 1b*	20	SITC 2025	ASCO 2026

* Planned based on data and available liquidity

Intellectual Property

Portage has licensed the rights to the adenosine antagonist from Impetis Biosciences Limited (Impetis) via its acquisition of Tarus Therapeutics. Impetus signed the license agreement with Impetis in October 2019. Rights were granted by Impetus to develop and commercialize the adenosine receptor antagonists for all indications. Under the license, Impetis is entitled to upfront payments of up to $38 million and royalties on worldwide net sales that begin in the mid-single digits and escalate through multiple tiers, with net sales over $1 billion receiving low double-digit royalties.

Portage has licensed the rights to its iNKT cell agonists from Ludwig Institute for Cancer Research Ltd. (Ludwig) via its acquisition of iOx. iOx entered into the agreement in July 2015. The license with Ludwig provides an exclusive worldwide license with the right to grant sublicenses to develop, make, have made, use, sell, offer for sale and import products as defined in the Ludwig license. Milestones of up to £20.45 million and low single digit royalties are owed on sales of relevant products. The royalty term extends for a period of ten years after first commercial sales.

Underlying patents and intellectual property protection has been secured or is pending in numerous jurisdictions including US, EU, Japan, Israel, New Zealand Great Britain, China and worldwide under Patent Cooperation Treaty (PCT) filing standards. The PCT is an international treaty that allows inventors to file a single patent application that can be used to obtain patent protection in multiple countries. Portage is further seeking patents that pertain to composition of matter, methods of manufacturing, sequences and structure, indications and other details specific to the manufacture, design and use of the associated compounds targeting the iNKT engagers and adenosine antagonists.

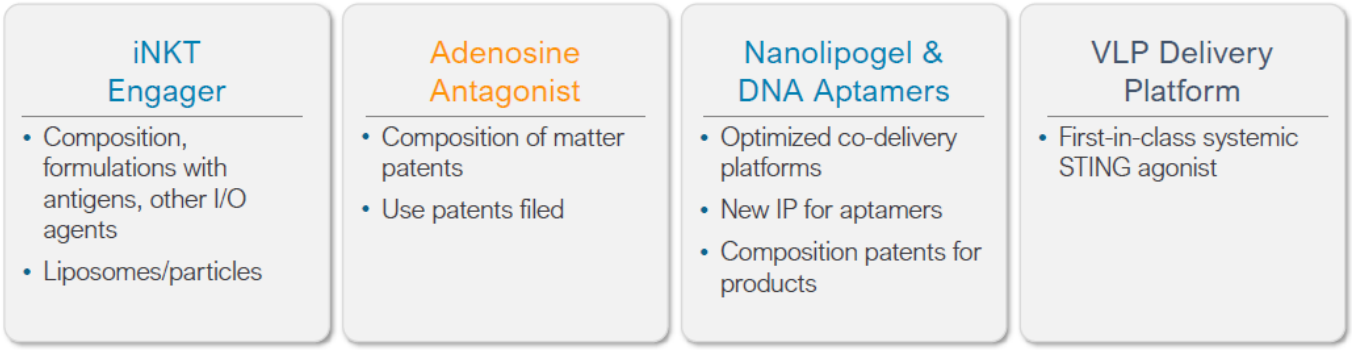
[15] Portage January 2024 Corporate Presentation

Exhibit X – Summary of Key Adenosine and iNKT Patents[16]

Compound	Title	Filed	Region	Expiry	Filer	Assignee	Link
Adenosine A2A	Fused tricyclic compounds as adenosine receptor antagonist	9/22/2011	Global	9/22/2031	Advinus Tx	Advinus	X
Adenosine A2B	Heterocyclic compounds as adenosine receptor antagonist	3/23/2009	Global	3/23/2029	Advinus Tx	Eurofins Advinus	X
Adenosine A2B	Substituted fused pyrimidine compounds	3/12/2010	Global	3/12/2030	Advinus Tx	Eurofins Advinus	X
Adenosine A2B	Purine compounds as prodrugs of a2b adenosine receptor antagonists, their process & medicinal applications	9/9/2009	Global	9/9/2031	Advinus Tx	Eurofins Advinus	X
iNKT	iNKT cell modulators and methods of using the same	11/30/2012	Global	11/30/2032	U of Birmingham Oxford	Ludwig	X
iNKT	Liposomal formulation of non-glycosidic ceramides and uses thereof	12/22/2011	Global	12/22/2031	Ludwig	Ludwig	X

Further detail summarizing the intellectual property (IP) position for Portage's platforms and products is included below. Over 60 patents have been issued around the globe with protection extending from 2031 to 2041. The protection spans not only the IP underlying the PORT-6 and PORT-2 programs but also other assets including non-lipogel and DNA aptamers and a stimulator of interferon genes (STING) asset.

Exhibit XI – Range and Depth of Intellectual Property Portfolio[17]



[16] Compiled by Zacks analyst
[17] Portage December 2023 corporate presentation

Primary Indications

Solid Tumors

Solid tumors consist of a broad variety of cellular growths that appear in different parts of the body including organs, muscles, bones, fat and cartilage. The tumors are abnormal masses of tissue that do not contain cysts or liquid areas. The neoplasms originate in sites including the breast, prostate, lung, colon, brain and other locations. Tumor growth is disorganized and irregular. It can spread to other parts of the body through the lymphatic system or bloodstream to distant sites where new tumors may be formed in a process called metastasis. Many factors contribute to or are associated with the genesis, presence and growth of tumors including genetics, age, lifestyle and environmental factors.

Solid tumors are more common than blood cancers and make up about 90%[18] of all cancers. The most common types of solid tumors are lung, breast, colorectal, prostate and skin lesions. In the United States there are about 2.0 million estimated new cases of cancer in 2023. Around the globe, there were about 18.1 million cases reported in 2020 by GLOBOCAN.[19] Some of the cancers most relevant to Portage's platforms include melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), breast cancer (BC), gastric cancer and prostate cancer.

Cancer is a disease that can affect any part of the body and is a group of diseases that is characterized by uncontrolled growth and spread of abnormal cells around the body. The normal process of regulated growth is disrupted and a mass of tissue is formed. Tumors can be either benign or malignant. Benign tumors do not invade nearby tissues and are unlikely to recur after removal. Malignant tumors present contrasting features such as invasion of nearby tissues, metastasis or spread to distant tissues, angiogenesis, anaplasia or poorly differentiated cells and genetic mutations.

Incidence & Prevalence

The Center for Disease Control and Prevention collects reported cancer cases and found 1.6 million new cases in 2020. This number underreported results for that year due to COVID-related disruptions and did not include contributions from Nevada and Indiana. Other resources such as the National Cancer Institute (NCI) find between 1.8 and 2.0 million cases of cancer per year and an incidence of 442.4 per 100,000 men and women.

According to the American Cancer Society, the prevalence of all cancers in males and females in the United States was about 18 million in 2022. Globally, almost 44 million persons are living with cancer in 2020 according to data synthesized from GLOBOCAN 2020 data and American Cancer Society Facts and Figures. Below we highlight some of the more common cancers that are amenable to candidates in Portage's portfolio.

Exhibit XII – US and Global Incidence of Various Cancers[20]

Indication	United States		Worldwide	
	Incidence/100,000	Population	Incidence/100,000	Population
NSCLC	40.9	238,340	12.2	2,206,771
RCC	14.9	81,800	4.6	431,288
Breast	118.8	297,790	12.5	2,261,419
Gastric	6.4	26,500	6	1,089,103
Prostate	99.4	288,300	7.8	1,414,259

Symptoms & Diagnosis

Cancer symptoms are frequently vague in the early stages making detection difficult. The most common are unexplained weight loss, fatigue, changes in bowel and bladder habits, unexplained pain, persistent cough, lumps or thickened areas in tissue, difficulty swallowing and persistent fever or night sweats among others. Many of the symptoms of cancer can also be related to other conditions, which requires medical guidance to identify the source. Persistent symptoms should be referred to a doctor to evaluate whether or not cancer is present.

[18] Based on analyst calculations using 2023 American Cancer Society New Cases.
[19] See the following resource for a thorough discussion of cancer incidence and mortality around the globe: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.
[20] Resources used: American Cancer Society, Ganti, *et al*., cancer.net, World cancer Research Fund International, Padala, *et al*., komen.org, seer.cancer.gov.

Cancer diagnosis requires procedures and tests to identify the presence of cancerous cells or tumors in the body. It begins with a review of the patient's medical history and a physical examination. Diagnostic and imaging tests may be run including X-ray, CT, MRI and PET scan and ultrasound. Blood tests may be run to measure blood count and identify tumor markers. A biopsy of the suspect tissue may be taken for further analysis in the lab. Depending on the type or site of the suspected cancer, other tests such as urine analysis, endoscopic exams or spinal tap may be performed. Genetic testing is also frequently run to identify gene mutations and to later identify personalized treatment.

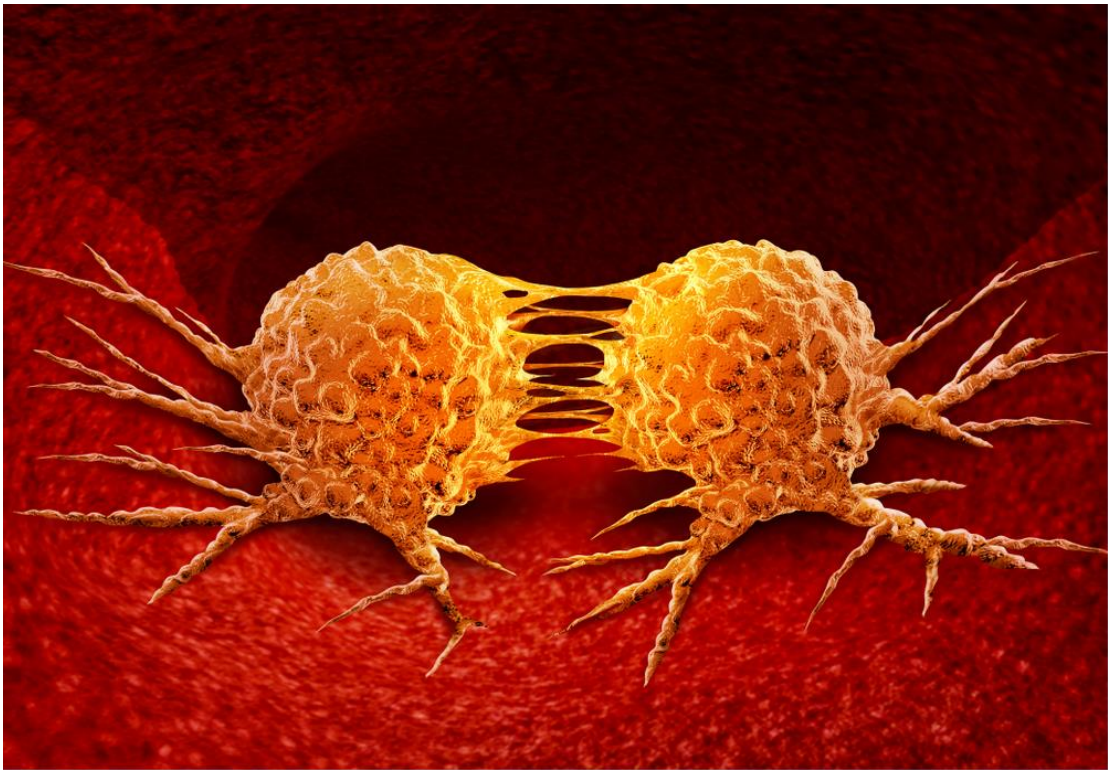
Current Standard of Care
Cancer treatment is highly dependent on the type and stage of the disease and patient characteristics. Surgery is frequently appropriate when the cancer has not spread and there are identifiable tumors. Chemotherapy is another common approach which uses drugs to destroy cancer cells and slow their growth. Radiation therapy is also commonly used, which directs high energy rays to kill cancer cells and shrink tumors.

Newer approaches such as immunotherapy and targeted therapy are appropriate. Immunotherapy uses the body's immune system to fight cancer. It includes various treatments, such as immune checkpoint inhibitors, CAR-T cell therapy, and other targeted therapies that help the immune system recognize and attack cancer cells. Many of these are discussed in the immuno-oncology section of this report. Targeted therapy uses drugs or other substances that identify and eradicate cancer cells based on their specific genetic or molecular characteristics. These treatments interfere with specific mechanisms involved in cancer cell growth and survival.

Other relevant types of treatment include hormone therapy for hormone-sensitive neoplasms such as breast, ovarian and prostate. Another newer approach, precision medicine, is used which identifies a patient's genetic makeup to develop a personalized treatment. Combination approaches are increasing in importance due to their ability to produce improved response and survival rates. Administering multiple agents is able to produce synergistic effects and overcome cancer resistance as it attacks the malignancy using various mechanisms of action. Another possible benefit is a reduction in side effects as lower doses of each agent may be used.

Some of the most important therapies (by revenues) for solid tumors include Merck's Keytruda, AstraZeneca's Tagrisso, Pfizer's Ibrance, Astellas' Xtandi, Roche's Perjeta and Johnson & Johnson's Erleada among numerous others. These newer agents are frequently used along with surgery, chemotherapy and radiotherapy.

Exhibit XIII – Dividing Cancer Cell[21]



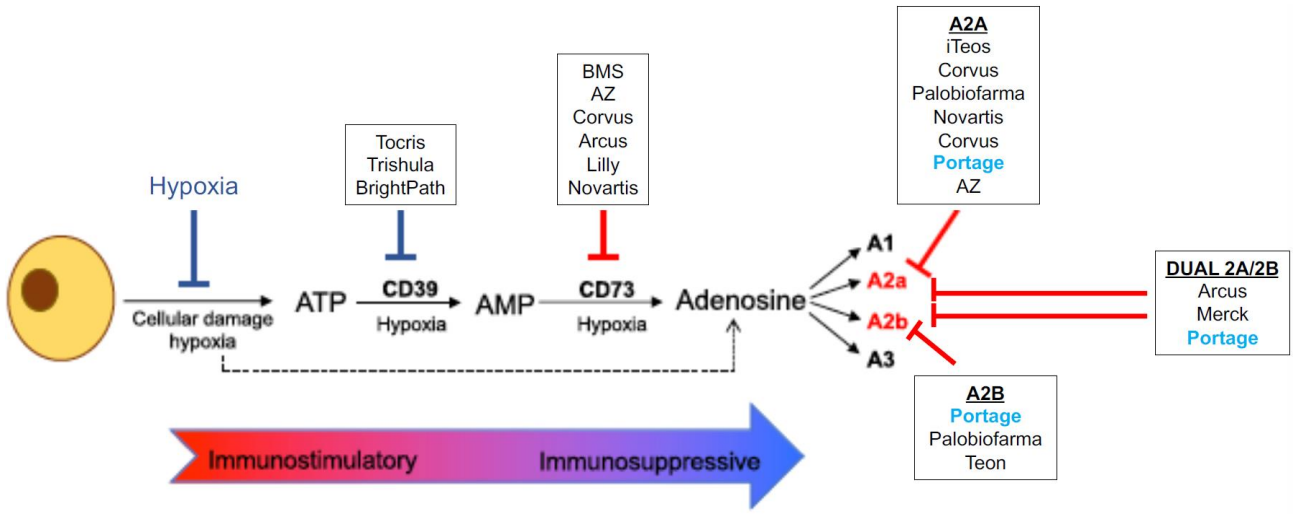
[21] Shutterstock. Image 1088678606

Peers and Competitors

Immuno-oncology is one of the most dominant areas in pharmaceuticals and biotechnology. Some of the leading technologies include checkpoint inhibitors, chimeric antigen receptor T-cell (CAR-T) therapy, personalized therapies, adoptive cell transfer, cancer vaccines and other approaches. Other important trends in the ecosystem include combination therapies and the use of biomarkers. There are numerous companies spanning the entire market cap range that are developing and commercializing I-O assets. This includes small names such as Portage up to the largest companies in the space such as Merck and Bristol-Myers Squibb.

In the adenosine antagonist universe, there are a number of competitors developing approaches throughout the adenosine signaling pathway. They start upstream with blocking CD39 and follow along the breakdown of ATP to adenosine to blocking the adenosine receptors themselves with Portage's asset among others.

Exhibit XIV – Sponsors Involved in the Adenosine Receptor Pathway[22]



Trishula Therapeutics is an oncology company developing TTX-030 to inhibit the production of adenosine in the tumor microenvironment using an anti-CD39 antibody. BrightPath Biotherapeutics is a Japanese company developing antibodies that target CD39 and CD73 to inhibit adenosine-producing enzymatic activity. CD73 is another target that is being pursued by several sponsors including Bristol Myers, AstraZeneca, Arcus, Eli Lilly and Novartis. Corvus Pharmaceuticals is broadly pursuing adenosine with programs that address both CD73 and the A2A receptor. Both programs are in early-stage clinical trials and are led by candidates mupadolimab and ciforadenant respectively. Mupadolimab is being used in patients with advanced NSCLC along with Keytruda. Ciforadenant is an antagonist of the A2A receptor, seeking to reverse the suppressive tumor microenvironment. This candidate is also being investigated in combination with checkpoint inhibitors. AstraZeneca is working on an A2A inhibitor in early-stage clinical trials for advanced solid tumors and prostate cancer. iTeos Therapeutics is another player with an A2A receptor antagonist. Its Phase II candidate, inupadenant, is targeting both high biomarker adenosine tumors and post I-O, chemotherapy naïve NSCLC. As with other A2A candidates, inupadenant will be studied in combination with other agents including Keytruda and chemotherapy. Portage is unique in the adenosine space in that it has a candidate for A2A, A2B and dual A2A/A2B targeting.

In the iNKT sphere, Portage is working on a pair of approaches that block adenosine production and activate iNKT cells. Others working here include GRI Bio, MiNK Therapeutics and Appia Bio. GRI is developing therapies to address chronic fibrotic diseases such as idiopathic pulmonary fibrosis, lupus nephritis and nonalcoholic steatohepatitis (NASH). Its therapies seek to regulate the NKT cells and sidestep unwanted immune responses that contribute to autoimmune disease. MiNK Therapeutics is a clinical stage precision oncology company developing allogeneic, iNKT cell therapies for cancer and other immune-mediated disease. The company's lead candidate, AGENT-797, is in Phase I/II studies with a checkpoint inhibitor for solid tumors. Appia Bio is a private company engineering an allogeneic CAR-NKT cell therapy derived from hematopoietic stem cells. The engineered CARs target the cancer. The company is in a preclinical stage of development with its CD19/CD20 CAR-NKT program which is partnered with Gilead's Kite division.

[22] Portage Adenosine KOL Event Presentation, March 2023

Exhibit XV – Peers and Competitors[23]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Therapeutic Area
1801.HK	Innovent Biologics	$38.40	$61,840	$57,240	PD-1 Tyvyt w / 4 indications approved in China, LAG-3, TIGIT, CTLA-4
208340.K	PharmAbcine	₩3,040	¥79,370	¥69,560	VISTA: PMC309. Also anti-angiogenesis VEGF(R2) & TIE2
600276.S	Jiangsu Hengrui	¥41.95	¥267,600	¥250,070	PD-1 (camrelizumab), PD-L1 (adebrelimab)
ABBV	AbbVie	$162.14	$291,852	$334,193	Oncology: hematologic malignancies, broad portfolio
AGEN	Agenus	$0.78	$297	$203	Checkpoint portfolio: PD-1, CTLA-4, TIM-3, LAG-3, TIGIT
ALLO	Allogene Tx	$2.91	$491	$25	Oncology: CAR-T, liquid & solid tumors
ALXO	ALX Oncology	$12.59	$627	$447	Checkpoint: CD47 - evorpacept
AMGN	Amgen	$303.00	$162,159	$186,458	VISTA asset through acq of "5' Tx"; no evidence pursuing
ATOS	Atossa Tx	$0.93	$117	$23	Hormone receptor breast cancer therapy
AZN	AstraZeneca	$68.38	$211,968	$228,981	Adenosine A2a (AZD4635) - dropped
BCAB	BioAtla	$2.38	$114	($27)	Conditionally active biologics: ADCs
BCYC	Bicycle Tx	$17.08	$513	($28)	Bicyclic toxin conjugate
BDTX	Black Diamond Tx	$2.73	$141	($3)	Precision onc, MasterKey Therapies target oncogenic mutation families
BEAM	Beam Tx	$26.07	$2,125	$1,109	Precision medicine; oncology & other
BGNE	BeiGene	$165.38	$15,763	$12,779	PD-1 tilelizumab (China) hepatocellular carcinoma
BMY	Bristol-Myers Squibb	$52.23	$106,275	$130,727	Opdivo, Yervoy. Relatlimab, lirilumab in dev.
CGEM	Cullinan Oncology	$10.17	$435	($31)	CLN081 small molecule in NSCLC w / exon 20 insertion mutations
CRIS	Curis	$12.60	$74	$6	CI-8993 for VISTA expressing cancers & other checkpoints
FATE	Fate Therapeutics	$3.77	$372	$22	Multiple targets (CD19/BCMA/HER2) in 5 oncology indications
GILD	Gilead Sciences	$83.31	$103,808	$121,057	Checkpoints: MB272, partnership w / Arcus anti-TIGIT & PD-L1
GMDA	Gamida Cell	$0.32	$34	$52	NK cell based immunotherapy
GRCL	Gracell Biotech	$10.03	$729	$499	CAR-T cell therapies
GRTS	Gritstone Bio	$1.96	$187	$132	I-O, cancer vaccines
GSK	GlaxoSmithKline	$39.21	$80,675	$92,280	PD-1 Jemperli dMMR endometrial cancer
INCY	Incyte Corp	$65.26	$14,625	$11,138	PD-1 retifanlimab & other PD-1 & PD-L1, TIM-3, LAG-3
INKT	MiNK Tx	$1.04	$36	$30	Expanded & CAR iNKT cells for solid tumors
INMB	Inmune Bio	$12.90	$232	$193	Cancer/Neurodegen-Reprogram innate immune system
IPHA	Innate Pharma	$2.92	$235	$185	Checkpoint: NKG2A target w ith monalizumab
ITOS	iTeos Tx	$10.70	$383	($216)	I-O pipeline: adenosine A2A antagonist (inupadenant)
IUGNF	Imugene	$0.09	$577	$475	I-O: HER-Vaxx, a HER2-positive cancer vaccine
KRON	Kronos Bio	$1.16	$68	($119)	I-O for solid & liquid tumors
LLY	Eli Lilly	$618.55	$587,194	$602,624	Broad I-O offering
MGNX	MacroGenics	$9.77	$606	$350	PD-1, CTLA-4, LAG-3, HER2, ADC, bispecifics,
MRK	Merck & Co.	$117.22	$297,038	$322,237	Keytruda. TIGIT (MK-7684) & LAG-3 (MK-4280) in development
MRKR	Marker Tx	$4.82	$43	$25	I-O: multi-tumor antigen approach
NKTR	Nektar Tx	$0.54	$102	($271)	IL-15 receptor agonists in dev. for liquid and solid tumors
NKTX	Nkarta Tx	$6.06	$297	$22	NK cell therapy in solid & liquid tumors
NUVB	Nuvation Bio	$1.49	$326	($293)	BET inhibition in solid tumors, drug-drug conjugates
NVS	Novartis	$106.31	$225,335	$230,708	Broad oncology portfolio
ONCY	Oncolytics Biotech	$1.26	$93	$63	Oncolytic virus for BC in combo w ith IO & targeted therapies
PFE	Pfizer	$29.47	$166,400	$183,267	PD-L1 Bavencio, PD-1 sasanlimab
RCUS	Arcus Bio	$17.73	$1,327	$528	Etrumadenant: dual A2a/A2b adenosine receptor antagonist
REGN	Regeneron	$913.17	$99,487	$92,276	PD-1 Libtayo, LAG-3 fianlimab, bispecifics
REPL	Replimune Group	$8.51	$503	$59	Oncolytic I-O, encodes checkpoint & expresses costimulatory factors
RGBP	Regen BioPharma	$0.71	$3	$3	Modulation of checkpoint protein NR2F6.
RHHBY	Roche	$37.03	$238,670	$259,700	Broad oncology portfolio: PD-L1 Tecentriq
RPTX	Repare Tx	$6.73	$284	$33	CRISPR enabled DNA damage repair approach in solid tumors
SNDX	Syndax Pharma	$21.49	$1,823	$1,449	Menin inhibitor for blood cancers
SNSE	Sensei Bio	$0.77	$19	($52)	SNS-101: VISTA for solid tumors. Also VSIG4 & CD39 targets
STTK	Shattuck Labs	$8.27	$351	$250	Agonist redirected checkpoint platform - oncology
TCRT	Alaunos Tx	$0.13	$32	$20	TCR-T cell therapy (KRAS, TP53, EGFR)
pvt	Appia Bio				CAR-engineered iNKT cells for cancer
pvt	Cellularity				Cell therapies-NK, CAR-T & ASCs. Cancer & degenerative disease
pvt	Kuur Tx				Off the shelf CAR-NKT cell therapies
pvt	Pierre Fabre Labs				anti-VISTA W0180, K01401
pvt	Syntrix Pharma				I-O to abrogate the immunosuppressive TME
PRTG	Portage Biotech Inc.	$1.09	$19.40	$16.20	Developing anti-VISTA candidate in Ph1/2

[23] Compiled by Zacks' analysts as of January 5, 2024

Financial & Operational Results

Milestones

- Name change to Portage Biotech – 2013
- Wholly owned subsidiary iOx Therapeutics obtains license for iNKT agonists – 2015
- Biohaven IPO & stock dividend to Portage shareholders – 2017
- SalvaRx iNKT platform acquisition – August 2018
- NASDAQ trading begins – February 2021
- First patient dosed in IMP-MEL (Phase I/II) PORT-2 (iNKT) program – August 2021
- Tarus Therapeutics acquisition for adenosine receptor agonists – July 2022
- Collaboration with Merck to evaluate PORT-2 in combination with pembrolizumab – November 2022
- PORT-2 Phase I/II interim data (iNKT) presented at ASCO – June 2023
- First patient dosed in Phase Ia PORT-6 (adenosine A2AR agonist) trial – June 2023
- Collaboration with Merck to evaluate adenosine agonists with pembrolizumab – September 2023
- $6.0 million direct offering – Autumn 2023
- Participation in SITC annual meeting – November 2023
- Two patients in PORT-2 combination trial dosed – November 2023
- Strategic update and shift in focus to PORT-6 & PORT-7 – January 2024
- ADPORT-601 (PORT-7) Phase Ia start – 1H:24
- ASCO Presentation ADPORT-601 for PORT-6 (Phase Ib interim) – June 2024
- ADPORT-601 (PORT-6) Phase Ib Start – 2H:24
- PORT-6/-7 pivotal studies - 2026

2Q:24 Financial Results

Portage reported fiscal year 2Q:24 results in a Form 6-K filing with the SEC on November 28th. For the quarter ending September 30, 2023 and the comparable prior year quarter, no revenues were reported. Loss for the second quarter totaled ($5.2) million or ($0.29) per share. Operational expenses rose 62% as increases in research and development (R&D) expenses were only partially offset by a decline in general and administrative (G&A) expenses.

- Research and development expenses totaled $4.2 million, up 171% from $1.6 million attributable to greater CRO related, clinical and manufacturing costs for the iNKT and adenosine programs. These increases were partially offset by lower payroll-related expenses;
- General & Administrative expenses were $1.7 million, down 19% from $2.1 million. Decreases in non-cash share-based compensation, insurance, directors' and officers' premiums contributed to the change;
- Other items of ($185,000) consisted of the non-cash loss from the change in fair value of the deferred price payable to former Tarus shareholders and the deferred obligation related to the iOx milestone and a decrease in foreign exchange transaction loss;
- Net interest expense totaled $43,000;
- Net income tax benefit of $0.9 million compares to $2.6 million with prior year period tax benefits related to currency effect;
- Net loss was ($5.2) million vs. ($1.1) million or ($0.29) and ($0.06) per share, respectively.

As of September 30, 2023, cash totaled $3.4 million. This amount compares to the $10.5 million balance in cash held at the end of fiscal year 2023 on March 31, 2023. Cash used in operations for 2Q:24 was ($4.3) million versus ($2.5) million for 2Q:23. Portage's cash as of September 30, 2023, together with the $6.0 million gross proceeds from the registered direct offering that closed subsequent to September 30, 2023 should be sufficient to support operations until calendar 1Q:24.

Management and Board of Director Profiles

Ian B. Walters, MD, MBA, Chairman of the Board and CEO

Ian B. Walters, M.D., M.B.A., is the CEO of Portage Biotech Inc. Over his 25-year plus career, he has demonstrated both leadership and expertise in drug development, including the advancement of multiple cancer compounds from research stages through regulatory approval.

Ian specializes in the evaluation, prioritization, and the innovative development of new therapies for the treatment of severe diseases. He has worked at PDL Biopharma, Inc., Millenium Pharmaceuticals, Inc. and Sorrento Therapeutics, Inc., leading corporate development, translational medicine, clinical development and medical affairs.

Ian spent seven years at Bristol Myers Squibb, where he managed physicians overseeing the international development of more than eight oncology compounds including Nivolimab (anti-PD-1), Ipilimumab (anti-CTLA-4), brivanib (anti VEGF/FGF), anti-IGF/IR, VEGFR2 biologic, Elotuzimab (antiCS1), as well as biomarker and companion diagnostic work. He was a core member of Bristol Myers Squibb's Strategic Transactions Group evaluating and executing licensing agreements, mergers and acquisitions, clinical collaborations and the company's immuno-oncology strategy.

Before entering the private sector, Ian was a lead investigator at the Rockefeller University and initiated advanced immunology research to understand the mechanism of action of several compounds. Ian received his MD from the Albert Einstein College of Medicine and an MBA from the Wharton School of The University of Pennsylvania. Ian is also a member of the board of directors of Enzo Biochem, Inc., a Nasdaq listed company, and BoKo Therapeutics. Ian is also a part-time consultant to Intensity Therapeutics, Inc.

Allan L. Shaw, Chief Financial Officer

Allan brings more than two decades of public company financial, operational, and strategic global business leadership. Allan serves as our CFO and is a five-time public company CFO with proven skills across multiple finance disciplines: corporate finance, capital markets and strategic transactions as well as a broad base of expertise in corporate governance and risk management. He structured, directed, negotiated and closed over $4 billion in public and private financings for several companies. Mr. Shaw has served on five public boards including chairing two audit committees, two compensation committees, and is currently involved with a portfolio of healthcare activities. Mr. Shaw is the founder and since 2005, has served as senior managing director, of Shaw Strategic Capital LLC, an international financial advisory firm focused on providing strategic financial counsel on a wide variety of issues such as general corporate finance, mergers and acquisitions, capital structuring, licensing and capital markets, and serving as financial consultant to private and public companies.

Mr. Shaw was the CFO and Treasurer of Syndax Pharmaceuticals, Inc. from January 2016 to February 2017 and from December 2011 to September 2015 was Managing Director of Alvarez & Marsal LLC, a global professional services firm, where he led their biopharmaceutical consulting practice. Additional prior experience includes serving as the CFO of Serono S.A. from November 2002 to May 2004, New Lead Holdings Ltd from October 2009 to July 2011 and Viatel, Inc. from November 1994 to June 2002. He currently serves on the board of directors of Calcimedica (Nasdaq: CALC) as an independent director and Edith & Carl Marks JCH of Bensonhurst, a non-profit organization, and chairs their finance committee. Mr. Shaw is a certified public accountant in the State of New York. Mr. Shaw received a B.S. from the State University of New York at Oswego College.

Robert Kramer, PhD, Chief Scientific Officer

Robert has 25 years of experience in the pharmaceutical industry and is the former Head of Oncology Discovery Research at both Bristol Myers Squibb and Janssen Pharmaceuticals, part of the Johnson & Johnson group of companies. He has been responsible for enabling the transition of 35 drugs from initial discovery into the clinic. Robert championed immunotherapy at Bristol Myers Squibb, which led, in 2009 to the acquisition of Medarex, Inc. and its portfolio of immune therapeutics that included Ipilimumab and Nivolumab. He received his PhD in pharmacology from the University of Vermont and undertook his post doctorate studies at the U.S. National Cancer Institute. Robert has also held an Assistant Professorship at the Harvard Medical School.

Steven Innaimo, Vice President of Project Management & Operations

Steven Innaimo is a seasoned research and development expert who brings more than 25 years of experience in drug development from the large pharma, biotech and contract research organization sectors. Prior to joining Portage in 2018, Steve spent two years at Covance as Executive Director and Head of the Global Project Management Office for Covance Clinical Development Services. He previously spent 23 years at Bristol Myers Squibb including his role as Senior Director of Oncology Project Management and Clinical Operations. During his time at Bristol Myers Squibb, Steve directly managed or provided development oversight for a number of immune-oncology assets, including Yervoy and Opdivo. He has driven multiple therapies to initial and post-marketing registrations globally. Steve began his research and development career as a molecular biologist for Targetech Inc.

Steve holds a B.S. in Molecular Biology, an M.S. in Endocrinology from the University of Connecticut and a Project Management Certificate from Boston University.

Brian Wiley, Chief Business Officer

Brian Wiley has nearly 30 years of experience in the biopharmaceutical industry, with over 25 years dedicated to oncology. His experience includes licensing deals, collaborations, M&A, both public and private financings and multiple product launches in oncology. He founded Boston BioConsulting, LLC, a consulting firm that specializes in corporate strategy, business development and pre-commercial planning for the biopharmaceutical industry. Additionally, he served as Chief Commercial Officer and Head of Business Development at NewLink Genetics and also served in various leadership and management roles at Celgene, Gloucester Pharmaceuticals, Millennium and Aventis.

Brian was awarded a B.A. in Marketing from Pennsylvania State University.

Justin Fairchild, Vice President of Development

Justin Fairchild has nearly 20 years of oncology drug development experience. Prior to joining Portage, Justin served as Vice President of Clinical Development at the Parker Institute for Cancer Immunotherapy, where he was responsible for a cross-functional team dedicated to the delivery of novel immunotherapy combination clinical trials. He also previously held several roles in both clinical operations and clinical development at Bristol Myers Squibb, where he contributed to both early- and late-stage studies of multiple targeted and immunotherapy oncology agents, including ipilimumab, nivolumab, dasatinib and cetuximab.

Justin earned an M.P.H. from The Johns Hopkins School of Public Health, and a B.A. in Chemistry from Colgate University.

RISKS

All investments contain an element of risk that reflects the uncertainty of a business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology have a much higher level of perceived risk.

The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical titans that have multiple products generating revenues, to small operations with a handful of employees conducting preclinical studies. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, some hazards are particular to smaller companies that have not yet established themselves or their products.

For smaller, early-stage companies, investing in drug development is a lengthy process. The timeframe for conducting pre-clinical research to eventually commercializing a drug can take from 12 to 15 years or even longer given market and company-specific conditions. And with, on average, only one in one thousand compounds eventually making it to the market from the preclinical stage, the risks are substantial.

Financing

Even if a company has a strong, experienced team that is developing a therapy with a high likelihood of success and a large addressable market, securing funding may be difficult. Access to financing comes and goes in cycles. During periods of improving confidence, capital may be easy to obtain; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. If capital is needed to sustain operations and it is not readily available, the company may be forced to suspend research and development activities, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route to progress or force a company to accept onerous terms.

Increases in cost of capital can make previously attractive investments less so. Interest rates have increased, materially changing the net present value and reward to risk ratio for many investments, especially those in higher risk categories such as drug development. Early-stage life sciences companies are dependent on a steady flow of capital to support their research and development activities. As capital becomes more dear, previously attractive projects may become less so, making access to critical capital inflows less certain. In addition to the cash carried on its balance sheet, Portage has access to a $50 million at-the-market facility with Cantor Fitzgerald and a $30 million committed purchase agreement with Lincoln Park Capital Fund subject to Baby Shelf Rule limitations. The company also holds approximately $5.6 million in Intensity Therapeutics shares which could be sold to raise capital.

Partners

Contract research organizations (CROs) have assumed a larger role in the development of drug candidates as the complexity and cost of trials has increased. Finding appropriate populations to participate in clinical trials has become increasingly difficult due to the shift to biomarker defined groups, personalized medicine and orphan indications that address small clusters of patients. This shift has increased the dependence on specialized CROs for project management and clinical monitoring services that add additional risks related to third parties. Portage in particular has relied on its CRO partners, Parexel International and Labcorp's Fortrea to help develop the adenosine and iNKT portfolios respectively.

Portage has entered into a clinical collaboration with Merck, which provides pembrolizumab for its Phase I/II combination studies with PORT-2, PORT-6 and PORT-7 in a variety of tumor types. Portage is responsible for conducting the related research and will share safety, tolerability, pharmacokinetic and anti-tumor activity of its candidates and pembrolizumab with its partner. Merck may withdraw its participation in the collaboration or refuse to make pembrolizumab available on favorable terms. Partnering with Merck for its PD-1 inhibitor may displace other potential combination partners that may have candidates with improved safety and efficacy when used with Portage's agents.

In March 2023, Portage's subsidiary Tarus entered into an agreement with Labcorp Drug Development (Fortrea) to provide services and support for the active Phase I/II adenosine clinical trial. Labcorp will assist in the effort to identify 10 clinical sites, screen, enroll and complete subjects, initiate and open clinical sites and monitor and validate data at each site. Labcorp will also provide support in preparing and developing interim safety data reports for review and analysis by the independent safety monitoring committee.

A CRO partner may face competing demands which can adversely affect the work they are managing on behalf of the client. CROs and subcontractors must abide by strict execution and trial parameters that if violated can jeopardize trial execution or data validity. Patient recruitment may be difficult. Subcontractors supervise and execute research as well as conduct biometric and pharmaco-vigilance, which are complex tasks. Clinical investigational centers need sufficient capacity and the candidate drug needs to be manufactured in compliance with current Good Manufacturing Practices (cGMP) and be available to administer to patients. Finally, the data itself needs to produce results that achieve sufficient statistical significance and clinical relevance to justify regulatory approval.

Regulatory Environment

All drugs must navigate the regulatory approval process in the US, EU, Japan and other countries before commercialization. Success is uncertain and may take years depending upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Isolating companies that have a history of research success in drug development, with opinion leaders and experts in the field are important factors that can help mitigate this risk. Companies and management teams that have achieved previous success with the FDA or other regulatory agencies are more attractive than those that are new to the process. Accelerated pathways to approval may be appropriate in some cases, such as those outlined in the Orphan Drug Act and the Breakthrough Therapy designation; however, changes in sentiment or perceived safety for pharmaceuticals drugs could alter the regulatory environment to demand a more thorough process and these pathways may be extended or additional requirements may be put in place. Portage has not indicated whether or not its adenosine blockers or IMM60 qualify for available expedited pathways.

Exhibit XVI – Success of Phased Trials and Regulatory Approval[24]

Phase	I - II	II - III	III - NDA/BLA	NDA/BLA - Approval	I - Approval
Probability	**52.0%**	**28.9%**	**57.8%**	**90.6%**	**7.9%**

Competitive Environment

Many firms are participating in the oncology space and products must compete against established treatments that are entrenched in the health care system. In oncology, for example, there are hundreds of approved agents available. According to Evaluate Pharma there are 211 marketed drugs in the immuno-oncology space as of January 1st, 2024. On the development side, there are 34 I-O agents filed, 221 in Phase III and 972 in Phase II. To differentiate itself from other sponsors, Portage has developed a platform to identify effective monoclonal antibodies with favorable side effect profiles. Its lead candidate is pursuing a broad mandate in solid tumors that do not respond to other therapies.

Marketing and Commercialization Risk

Successful marketing of approved drug candidates relies on adoption by patients and providers. An approved drug must have convincing clinical trial data and maintain a favorable reputation among prescribers. Marketing is expensive and requires an experienced sales force and a presence in the marketing region. Marketed products remain under surveillance and any unexpected adverse effects may lead to regulatory authorities revoking marketing authorization. Inclusion of the drug in insurance plan offerings is also important. Rapidly obtaining a preferred position on health plan and payor formularies is critical to achieving target penetration rates. If health plans and payors cannot agree on appropriate pricing for the drug and the compound fails to offer a significant benefit above standard of care, sales may be limited. Portage is several years away from marketing and commercialization activities. We anticipate that the company will hand off the assets to a larger partner who will advance these activities.

Manufacturing

Medical product companies can either produce medicines in-house or rely on third parties to manufacture them. While there are many benefits to owning manufacturing facilities and exercising direct control, in most cases small and medium size biopharmaceutical companies work with partners through supply agreements to make their products. Working with a partner confers several benefits including economies of scale, a management team dedicated to compliance with regulatory requirements and the flexibility of engaging other manufacturers based on changing circumstances. The use of a partner also limits the capital burden of a single product company and more closely aligns volume, costs and their respective timing. While there are numerous benefits to outsourcing manufacturing, a sponsor can also be exposed to several risks. Manufacturing partners may not prioritize client projects and may run

[24] Summarized from Clinical Development Success Rates 2011-2020. Compiled by Zacks Analysts.

afoul of regulatory requirements. The manufacturer may experience quality control or volume constraints that could disrupt demand. Take or pay contracts could force the client to accept more product than can be sold in a reasonable time, impacting cash flow and producing excessive inventory which could expire before sale. Portage has engaged Evonic Industries and ASCHEM GmbH to manufacture and perform biologics development for the iNKT program. Eurofins Scientific and Almac Group are performing the same services for the adenosine programs. Manufacturing services are mostly conducted in Europe.

Intellectual Property

Despite the existence of patents, exclusivity and trade secrets, infringement of intellectual property is a risk. In July 2022, Portage acquired Tarus Therapeutics which had signed a license agreement with Impetus Biosciences. The Impetus agreement granted Tarus an exclusive worldwide license to develop and commercialize adenosine receptor agonists for specific indications. In return for the license, milestones and royalties will be owed.

Portage's intellectual property related to the iNKT platform was licensed through its ownership in iOx from the Ludwig Institute for Cancer Research. The license provides certain technology, intellectual property and know-how and development with respect to iNKT cell agonists to treat human diseases. Ludwig granted iOx an exclusive worldwide license and the right to grant sublicences to develop and commercialize products based on this technology. A royalty is owed to Ludwig for ten years after first commercial sale.

Portage relies on the licensed intellectual property (IP) to protect its adenosine and iNKT assets that address composition of matter, methods of manufacturing, indications pursued and other elements. The company is both licensing IP and developing new IP to register worldwide. While the protective patents can prevent others from using the same technology as used in PORT-2, PORT-6 and PORT-7, other approaches centered on the same targets may be successfully pursued that do not violate the licensed property. Portage may also pursue patent term restoration along with the regular life of a patent, which is 20 years. Patent term restoration compensates for the time lost during the regulatory approval process.

Geopolitical

Recent trade tensions between the US and China threaten the world economy and were exacerbated by the COVID pandemic. There had been a cross-pollination of capital and drug development between China and the United States which has slowed as a result of the trade and political dispute between the countries. This conflict may reduce the availability of capital, partnerships and future development and commercialization deals between companies in the two nations. The UK withdrew from the European Union in 2020, creating new trade, transportation and other barriers between the UK and mainland Europe. The European Commission Decision Reliance Procedure, which allows the UK regulatory apparatus to rely on EU centralized marketing authorization decision, has expired. Following this date, sponsors must obtain UK marketing authorization for product sales in the UK. The war between Ukraine and Russia has disrupted clinical trials in these countries. Sanctions have also been placed on Russia and many of its businesses which may lead to product shortages. Refugees fleeing the war in Ukraine may also impact nearby countries and their productivity which could affect clinical trials and commercialization in these areas.

Inflation

Drug price inflation has gained attention as it and other health care costs have risen at a materially faster pace than the consumer price index. As new therapies have been approved, drug prices have increased to reflect higher development costs and improved pricing power of pharmaceutical and biotech companies. On the demand side, deductibles have been steadily increasing over the last decades, and in some cases, individuals and families must cover several thousand dollars in costs before the benefits of insurance begin. Cost sharing or co-insurance is another component of insurance plans that directly increases the burden on patients. This has resulted in greater elasticity in demand for drugs than was previously the case. Individuals with high deductibles or no insurance may be sensitive to price and avoid treatments with high cost.

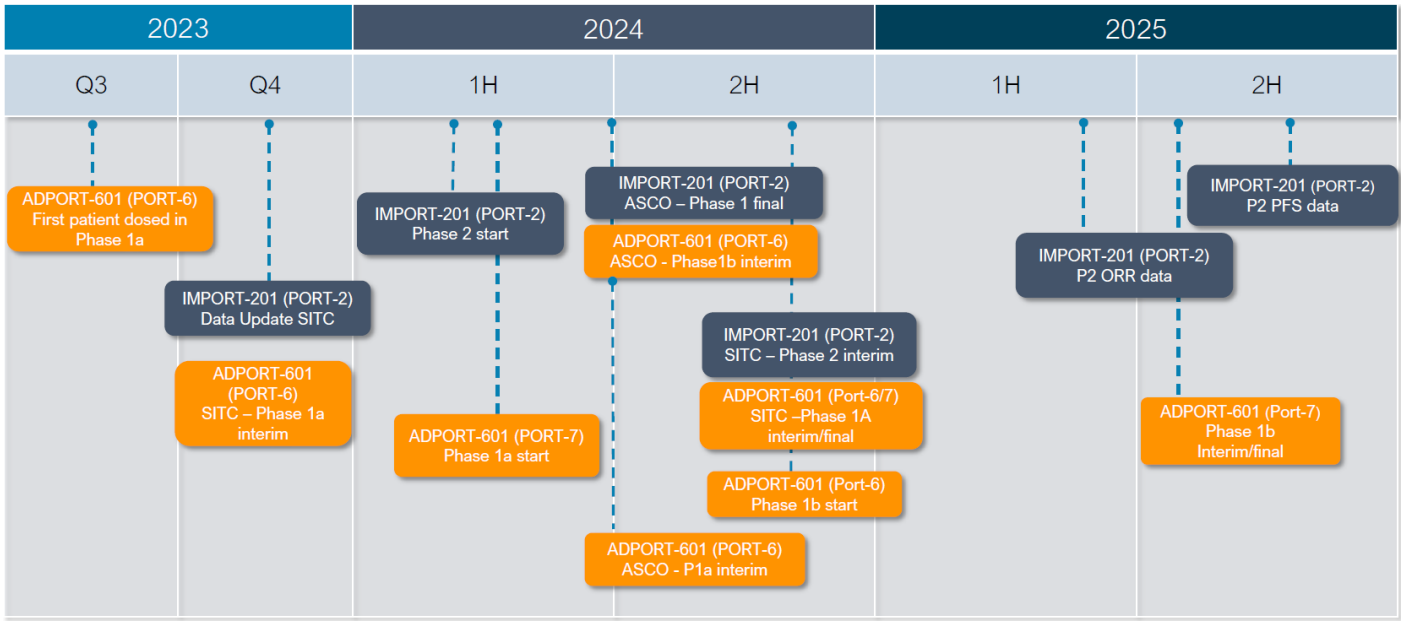
While we have discussed a broad variety of risks above, we believe that our forecast parameters, discount rates, success probabilities and valuation metrics address these potential outcomes and our target price reflects an assumption of these risks faced by biotechnology companies.

VALUATION

Portage has thrown its research and development efforts behind its adenosine antagonists. While the PORT-2 iNKT engager remains in the pipeline, we will not value the program as company resources have been shifted to PORT-6 and PORT-7. The adenosine signature has been identified in many types of solid tumors including colorectal, head and neck, lung, stomach and esophageal cancers. It also appears in many other malignancies. Adenosine signature cancers are amenable to combination therapy and we anticipate that products approved in indications where checkpoint inhibitors are and are *not* used comprise the appropriate addressable market. Given the potential broad applicability of the adenosine candidates, we model a conservative penetration into solid tumors as a whole and anticipate expanding this as new data further defines the addressable market.

PORT-6 and PORT-7 are subjects of a Phase I/II trial and are undergoing dose escalation and dose expansion studies both as monotherapy and in combination with Merck's Keytruda. We anticipate that interim and final Phase Ia data will be reported in 2024 followed by the start of the Phase Ib in late 2024. A pivotal trial is expected to start in 2026 and complete by 2027. PORT-6 is anticipated to be the subject of a new drug application (NDA) and a marketing authorization application (MAA) with the FDA and EMA respectively in 2028. Commercialization is forecast to begin in 2029.

Exhibit XVII – PORT-6 and PORT-7 Development Milestones[25]



This pathway may be accelerated if Portage is able to secure expedited treatment for its drug application. If the PORT-6 and PORT-7 indications are considered serious conditions or unmet medical needs or if either offers a substantial improvement over existing therapy, Fast Track or Breakthrough Therapy may be granted and could accelerate the timelines we predict. Accelerated Approval may also be granted which would allow a surrogate endpoint such as progression free survival (PFS) or durable response to be used rather than overall survival (OS). Portage may also be acquired prior to producing pivotal results and under the direction of a larger company with more resources could accelerate the timelines we forecast.

Our addressable market includes the entire annual incidence of solid tumors which is approximately 2 million in the United States and 16 million outside of the US. The model reflects sales from the US and rest-of-world which totals 18 million cases. Population growth is forecasted at 0.5% in the US and 1.0% in the rest of the world. Drug price inflation is expected to be 2.5% in the US and 1.5% in the rest of the world.

In the United States we assume a penetration rate of 0.15% of the solid tumor cancer population in 2031, growing to 0.50% by year seven. This equates to 3,100 patients treated in year one and 10,600 in year seven. We estimate that patent and other IP protection will lapse after 2041 and reflect a decline in sales over the next four years. We assume pricing for small molecule PORT-6 will be $70,000 in 2029 growing at 2.5% annually. Our thesis relies on a

[25] Portage December 2023 corporate presentation

large pharmaceutical partner obtaining rights or buying out Portage prior to commercialization. Due to the anticipated differentiated mechanism, anticipated multiple bidders and combination of favorable safety and efficacy, we assume a royalty (which is inclusive of upfronts and milestones) of 35%, which represents the entirety of economic value received for the asset. We net out 8 percentage points to reflect the royalty owed to Impetus Biosciences, which estimates future milestones in a mid-single digit royalty on amounts below $1 billion and a tiered royalty of low double digits above sales of $1 billion. This produces a net royalty of 27% to Portage. These assumptions generate royalty income of $58 million in year one and $232 million in year seven (2035).

In the rest-of-world, we assume a first-year penetration rate of 0.09% into the solid tumor population in 2029, growing to 0.30% by year seven. This equates to 15,000 patients in year one growing to 54,000 by year seven. We estimate that global intellectual property protection will begin to roll off by 2041, and forecast a decline in sales over the following four years. Pricing for the asset outside of the US will be at half of US levels or $35,000 per course of treatment growing at 1.5% annually. As with the economic value extracted by Portage in the US, we assume that the net 27% royalty will carry over to the international sphere as well. These assumptions generate royalty income of $144 million in 2029 and $568 million by year seven (2035).

Estimates for operational costs call for $15 million in cash expense for FY:24, $17 million in FY:25 and $19 million in FY:26 after which costs are estimated to grow at a low-single-digit per annum rate. Following commercialization, research and development amounts are predicted to fall to zero. After first profits are generated, net operating losses will be consumed. After NOLs are exhausted, we forecast a 25% cash tax rate on earnings. After tax cash flows to the company are discounted at a 15% rate with a terminal growth rate of -10% beginning in 2046. We apply an overall 20% likelihood of success given the stage of development, early results and data generated by other candidates in the class.

Option and warrants are assumed to be exercised if below our target price with proceeds added to cash and exercised shares added to shares outstanding. In addition to the approximately 21 million shares of common stock and pre-funded warrants and 9.5 million exercised warrant shares, we add an additional 10 million shares to reflect potential capital raises over the next 18 months. Shares used to calculate our target price are approximately 39.3 million.

Despite the conservative stance of our assumptions, penetration into addressable markets can potentially be higher for PORT-6 if study results demonstrate strong efficacy, synergy with other agents, safety and success in additional indications. We note that the determinant for many of the variables in our model will be the ultimate performance of Portage’s candidates in the clinic and in pivotal studies. We will update our model accordingly as data is made available and if other assets in the pipeline are advanced towards the anticipated new drug application.

Based on the assumptions identified in our discounted cash flow model, we generate a valuation of $7.00 per share.

CONCLUSION

Portage is developing two platforms that address adenosine blocking and iNKT agonism. Both are promising platforms that appear to work well with other immunotherapies such as checkpoint inhibitors. Portage is focusing on the adenosine A2A antagonist with its PORT-6 asset and is now conducting Phase I/II studies. Many studies have shown a synergy between adenosine antagonists and checkpoint inhibitors, which makes the asset particularly attractive to large pharmaceutical companies that have dominant checkpoint inhibitor franchises that may lose their intellectual property protection in coming years.

Portage's PORT-6 asset is differentiated from other A2A receptor antagonists due to its improved potency, selectivity and durability. In addition to an improved asset, Portage plans to employ an immunohistochemistry-based biomarker that should improve the selection of patients that will respond best to the therapy. The biomarker may also define the population where PORT-6 may be approved. Adenosine A2A inhibition in the tumor microenvironment is also a safe approach that does not interfere with the physiologic role of adenosine in critical functions. PORT-6 acts downstream of other therapies that seek to block CD39 or CD73, which could have unintended off target effects. Its specificity also avoids binding to A1 and A3 receptors which are predominantly oriented outside the boundaries of cancer and involved in neuronal activity and neuromodulatory signaling.

PORT-6 has moved into the clinic and is the subject of a Phase Ia/II dose finding study that will identify the recommended Phase II dose. Further studies will evaluate PORT-6 both as monotherapy and with other checkpoint inhibitors. Blocking the A2A receptor on a variety of cells in the tumor microenvironment can increase cytotoxicity, improve effector function, increase inflammatory response, enhance T cell activation and promote phagocytosis among other benefits. Many of these effects potentially increase the utility of checkpoint inhibitors and other immunotherapies. High adenosine expression is found in a wide variety of cancer types, including renal cell, breast, lung, gastric and prostate cancer with all indications potentially candidates for approval following further clinical trials. A biomarker defined population may also be approved, similar to approvals for cancers with PD-L1 expression, MSI-high or HER2 overexpression.

PORT-6 is Portage's lead candidate and the subject of an ongoing Phase I/II clinical trial that is now performing dosing studies. PORT-7 dosing is expected to begin shortly. The multi-phase trial is expected to be conducted over the 2024-2025 period and generate data that will confirm the initial indications that will be pursued. We expect that Portage will continue clinical trial work to add more indications as R&D efforts advance. Although our model does not include any expedited treatment for PORT-6, strong initial data in the Phase II may support the use of the Fast Track and Accelerated Approval pathways, which could hasten commercialization.

Many cancers are not cured with first line therapy and patients move into second, third and later line therapies to eradicate resistant tumors. This provides a large unmet need that new combination therapies may address. Based on our review, there are about two million new solid tumor cases in the US and 16 million outside the US. While Portage will initially be focused on a subset of all solid tumors, the potential could be greater as almost all tumors express adenosine, which contributes to cancer growth and metastasis. Our model anticipates a low penetration rate into the broad indication of solid tumors; an opportunity set that we will refine as the ultimate approved indications become clearer. Pricing for a course of therapy is expected to be in line with other small molecule immunotherapies and sales are forecast to generate royalty and other related revenues for Portage through a partner's commercialization activities.

Portage has recently raised capital and has access to other sources of funding including an ATM, a committed share purchase agreement and ownership in shares of a public company that can fund research and development activities. Cash burn is estimated to be under $4 million per quarter, which suggests sufficient funding to support operations into early 2024.

Key reasons to own Portage shares:

- **Experienced pharmaceutical management team with development & commercialization successes**
  - **Bristol Myers Squibb, Johnson & Johnson,**
  - **Strong academic & industry network**
  - **Team members have obtained approval for multiple assets**
- **Product focus on candidates that address known resistance in approved therapies**
- **Two platforms with multiple clinical studies underway**
  - **Anti-adenosine platform featuring PORT-6 (TT-10) and PORT-7 (TT-4)**
    - **Targets A2A & A2B expressing solid tumors alone and with Keytruda**
    - **Reverses immunosuppressive tumor microenvironment**
    - **No dose limiting toxicities observed**
    - **May seek approval in biomarker defined population**
  - **iNKT engager (PORT-2)**
    - **Offers features of both natural killer and T cells**
    - **Stimulates innate and adaptive immune system for anti-cancer response**
    - **Evaluated alone and in combination with Keytruda**
- **Offers additional assets on featured platforms**
  - **PORT-3 – includes combination of PORT-2 with vaccine**
  - **A2A/A2B dual antagonist**
  - **Gut-restricted A2B antagonist**

PORT-6 adds another compelling entry into the immuno-oncology universe and has shown promising activity in combination with checkpoint inhibitors in pre-clinical and with similar assets in competitor studies. Our valuation work takes into account commercialization of the asset around the globe, assuming a 20% probability of success. As PORT-6 and PORT-7 progress and generate additional data, we will refine our model accordingly. We initiate on Portage Biotech, Inc. with a target price of $7.00 per share.

PROJECTED FINANCIALS

Portage Biotech Inc. - Income Statement

Portage Biotech Inc.	2023 A	Q1 A	Q2 A	Q3 E	Q4 E	2024 E	2025 E	2026 E
Total Revenues ($USD)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Research & Development	$8,214	$3,627	$4,237	$4,100	$3,000	$14,964	$11,820	$12,850
General & Administrative	$8,361	$1,370	$1,693	$1,400	$1,400	$5,863	$5,600	$6,620
Income from Operations	($16,575)	($4,997)	($5,930)	($5,500)	($4,400)	($20,827)	($17,420)	($19,470)
Other Items	($106,155)	($1,154)	($185)	$0	$0	($1,339)	$0	$0
Net Interest Expense	$208	$80	$43	$40	$50	$213	$200	$200
Pre-Tax Income	($122,522)	($6,071)	($6,072)	($5,460)	($4,350)	($21,953)	($17,220)	($19,270)
Provision for Income Tax	$17,856	$145	$907	$0	$0	$1,052	$0	$0
Net Income	**($104,666)**	**($5,926)**	**($5,165)**	**($5,460)**	**($4,350)**	**($20,901)**	**($17,220)**	**($19,270)**
Reported EPS	**($6.49)**	**($0.33)**	**($0.29)**	**($0.28)**	**($0.22)**	**($1.11)**	**($0.69)**	**($0.55)**
Basic Shares Outstanding	16,119	17,701	17,801	19,700	19,850	18,763	25,000	35,000

Source: Company Filing // Zacks Investment Research, Inc. Estimates

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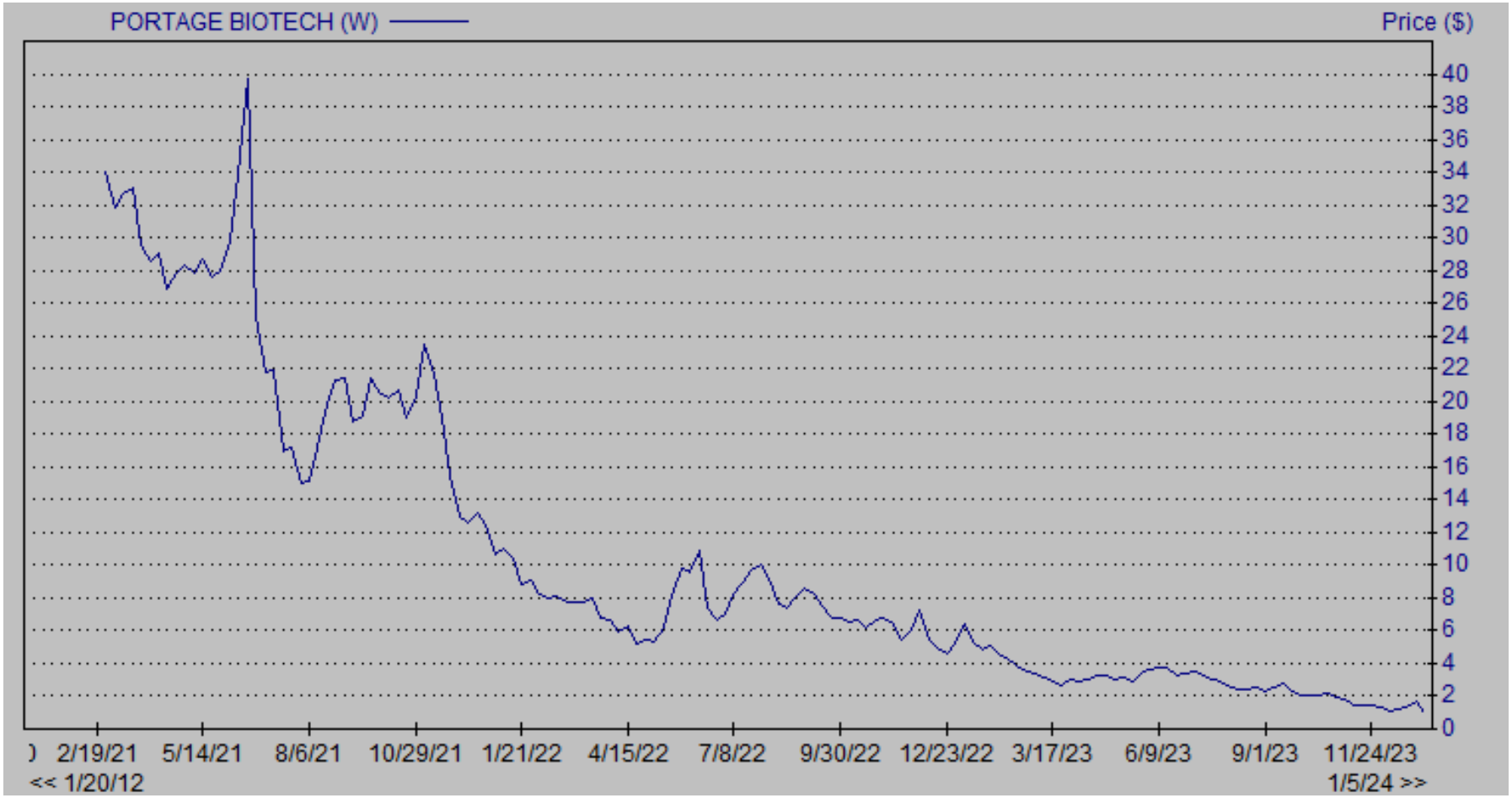
HISTORICAL STOCK PRICE

Portage Biotech Inc. – Share Price Chart[26]



[26] Source: Zacks Research System

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