Kairos Pharma, Ltd. (KAPA)
Rating: Buy

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Attacking Cancer Rx Resistance and Boosting Immune Function; Initiating at Buy and $12 PT

Stock Data	4/2/2025
Price	$0.92
Exchange	NASDAQ
Price Target	$12.00
52-Week High	$4.00
52-Week Low	$0.85
Enterprise Value (M)	$10
Market Cap (M)	$13
Shares Outstanding (M)	13.7
3 Month Avg Volume	2,312,231
Short Interest (M)	0.03
Balance Sheet Metrics	
Cash (M)	$3.2
Total Debt (M)	$0.1
Total Cash/Share	$0.23

EPS ($) Diluted			
Full Year - Dec	2024E	2025E	2026E
1Q	--	(0.08)	--
2Q	--	(0.10)	--
3Q	(0.10)A	(0.09)	--
4Q	(0.08)	(0.14)	--
FY	(0.13)	(0.42)	(0.40)

Revenue ($M)			
Full Year - Dec	2024E	2025E	2026E
1Q	--	0.0	--
2Q	--	0.0	--
3Q	0.0A	0.0	--
4Q	0.0	0.0	--
FY	0.0	0.0	0.0

Public statements available from 3Q24

Oncology pipeline could unlock the immune system to overcome cancer resistance in mCRPC and beyond. We are initiating coverage of Kairos with a Buy rating and $12 PT. Kairos is a clinical stage company developing a novel class of drugs targeting cancer drug resistance and checkpoints of immune suppression. Despite the significant advances made with the advent of immunotherapy, low response rates and treatment resistance remain common challenges in the treatment paradigm. To combat this, Kairos has discovered a potential central resistance mechanism utilized in multiple cancer types via the upregulation of CD105 (endoglin). Kairos' lead asset, ENV-105 (an anti-CD105 antibody) is currently in clinical development to treat metastatic castration resistant prostate cancer (mCRPC) and non-small cell lung cancer (NSCLC). Endoglin upregulation as a cancer drug resistance mechanism has been implicated across multiple tumor types and a variety of treatment modalities, including hormone and EGFR therapy, as well as in the resistance developed against radiation and chemotherapy, underscoring the potential of ENV-105 in further indications including colon, breast and head and neck cancer tumors. Beyond ENV-105, the company also boasts a robust pipeline of preclinical candidates that specifically target immune checkpoints across a range of solid tumor and autoimmune indications. With two clinical catalysts poised for readouts 2025 (interim Phase 2 data in mCRPC in 1H25 and initial Phase 1 NSCLC by YE25), and several preclinical candidates nearing IND-stage, we foresee significant newsflow and long-term value for investors that enter at this stage. We currently emphasize the imminent Phase 2 interim readout for ENV-105 in mCRPC, as we believe this will represent a significant de-risking event for investors.

Turning back the hands of the cancer drug resistance clock with ENV-105. The goal of the ENV-105 program is reversing cancer drug resistance (i.e. those acquired through hormone therapy, radiation, I.O. etc.) by exploiting synthetic lethality, re-sensitizing patients, and enabling cancer drugs to last longer. A notable feature we highlight, is that ENV-105 adds to the treatment armamentarium by reviving the current SOC treatments (i.e. Xtandi for mCRPC and Tagrisso for EGFR-driven NSCLC) without introducing a brand-new modality per se. As a combination therapy, ENV-105 could be used to improve or extend the efficacy of such blockbuster drugs in their respective indications, providing a unique market opportunity. Here, we see ENV-105 as being leveraged by big pharma to enhance their existing oncology pipelines, providing unique partnering/collaboration opportunities. Currently, ENV-105 drug seeks to address unmet medical needs in the large markets of prostate and lung cancers. For example, the global prostate cancer therapeutics market size is valued at $12.4 billion and at $4 billion for EGFR mutant NSCLC, representing a significant opportunity for Kairos to strategically position itself.

Bench to bedside in a one-stop shop; strategic relationship with leading academic hospital and extensive IP portfolio fortifies pipeline development. Kairos is helmed by pioneers in the field of cancer therapeutics, including CEO Dr. Jonathan Yu, a leading oncologist/surgeon at Cedars-Sinai Medical Center in Los Angeles specializing in glioblastoma treatment and CSO Dr. Neil Bhowmick who has discovered many of the scientific advancements utilized in the Kairos pipeline, which we detail in this report. The science underlying the intellectual property was also developed at Cedars-Sinai Medical Center. Kairos licensed patents from Cedars-Sinai Medical Center and Tracon Pharmaceuticals (TCON; Not Rated), from which it acquired ENV-105 (previously TRC105). Here we note that as part of its licensing agreement with Tracon, ENV-105 comes partially de-risked to Kairos as it was previously studied in a small Phase 2 proof-of-concept study. Both ongoing clincial studies of ENV-105 are also being run at Cedars-Sinai, with additional centers being actively brought online. Kairos has an extensive IP portfolio of seven drug candidates, valid until 2040, which offers diversification and mitigates the overall exposure to many of the inherent risks of drug development.

Kairos' companion biomarker is an underappreciated strategy that could be a key to success. Another aspect of Kairos' development strategy worth highlighting with investors, in our opinion, is the inclusion of biomarker analysis in the ongoing ENV-105 clinical studies. A three-gene panel was identified to serve as a companion biomarker for patient selection, by distinguishing potential drug responsive and non-responsive patients, prior to therapy, based on the biomarker gene expression levels. Currently under co-development with the Kairos subsidiary, Enviro (acquired in 2021), we see the companion biomarker test as a significant value-add to the ENV-105 program as a means to further ensure successful clinical development and outcomes through to the NDA and FDA approval process. The biomarker test development is further supported by a $3.2 million NIH grant to Kairos CSO, Dr. Bhowmick, which will be used and verified in the ongoing multi-center randomized Phase 2 trial of ENV-105 in mCRPC as well as the randomized Phase 1 study in NSCLC. This diagnostic will seek FDA approval as a critical tool for the identification of suitable patients with mCRPC or EGFR-mutated NSCLC, guiding inclusion for treatment in Phase 3 clinical trials and strengthening an overall regulatory package as trials progress.

Diversified pipeline with transformative potential in oncology and autoimmune indications; KROS-101 set to enter clinic in 2026. While the two ENV-105 clinical program are the primary drivers of our Kairos investment thesis, the company is concurrently progressing several preclinical assets including, KROS-101 (a GITR agonist) and KROS-102 (a GITR antagonist). KROS-101 is being developed as a systemic immune modulator to address immunosuppressive activity of solid cancers. When thinking of how KROS-101 could be added to the current cancer treatment landscape, there could be a viable opportunity in combination with checkpoint inhibitors. Namely, by increasing T cell numbers and function KROS0101 may complement checkpoint inhibitors like pembrolizumab (Merck; MRK; not rated) and nivolumab (Bristol-Myers Squibb; BMY; not rated). Acting in an opposing fashion to KROS-101, KROS-102 is a GITR ligand antagonist designed to increase the inhibitory regulatory T cell functions while hampering T effector cell (killer T cells) numbers and function, which could reduce the overactive immune response observed in autoimmune diseases. By using the same mechanism of controlling T cell growth as KROS-101, but in the opposite direction, KROS-102 reduces T cell numbers and activity to potentially become a new class of agents for autoimmune diseases and transplant rejection. Given the market opportunity and large indications that KROS-102 could target, we envision a partnership with Big Pharma as a potential path forward. Currently in DMPK studies, the company first expects to advance KROS-101 to the clinic in early 2026 as part of a Phase 1 monotherapy study. Although we do not currently include these assets in our NPV, we maintain they represent significant clinical and commercial potential that should be on investors' radar.

Valuation and Risks. We are instituting a Buy rating and $12 price target. Our valuation is based on our clinical net present value (NPV) model, which allows us to flex multiple assumptions affecting a drug's profile. We consider two key factors when considering our valuation of Kairos using our NPV approach:

- We only value ENV-105 for mCRPC for the U.S. market (20% PoS 100% contribution), which has the potential to be a blockbuster indication for Kairos. We feel we are being conservative in our market model approach of ENV-105 by only attaining ~20% market penetration and ~$700 million peak sales, while still representing an unmet medical need.
- We purposefully omit the rest of Kairos' pipeline, including ENV-105 for NSCLC, which is already in the clinic. This represents a not only an additional layer of conservatism, but provides significant upside potential over the long-term by having multiple opportunities increasing the changes of potential success, in our belief.

Factors that could impede reaching our price target include failed or inconclusive clinical trials, the inability of the company to secure adequate funding to progress its drug through the development pathway or the occurrence of dilutive capital raises.

Company Background

Kairos Pharma is a clinical-stage biopharmaceutical company developing a portfolio of therapies designed to overcome drug resistance and immune suppression in oncology, two critical areas that despite recent advances, continue to challenge effective cancer treatment. To combat this hurdle, the company has built out a pipeline of assets including antibodies and small molecules for a range of solid tumor indications, including prostate cancer, lung cancer, breast cancer and glioblastoma. The company's assets were developed and licensed from Cedars-Sinai Medical Center in Los Angeles, with which the company has since launched a strategic relationship supporting clinical trial efficiency and therapeutic innovations. The company is helmed by pioneers in the field of cancer therapeutics, including CEO Dr. Jonathan Yu, a leading oncologist/surgeon at Cedars-Sinai Medical specializing in glioblastoma treatment and CSO Dr. Neil Bhowmick.

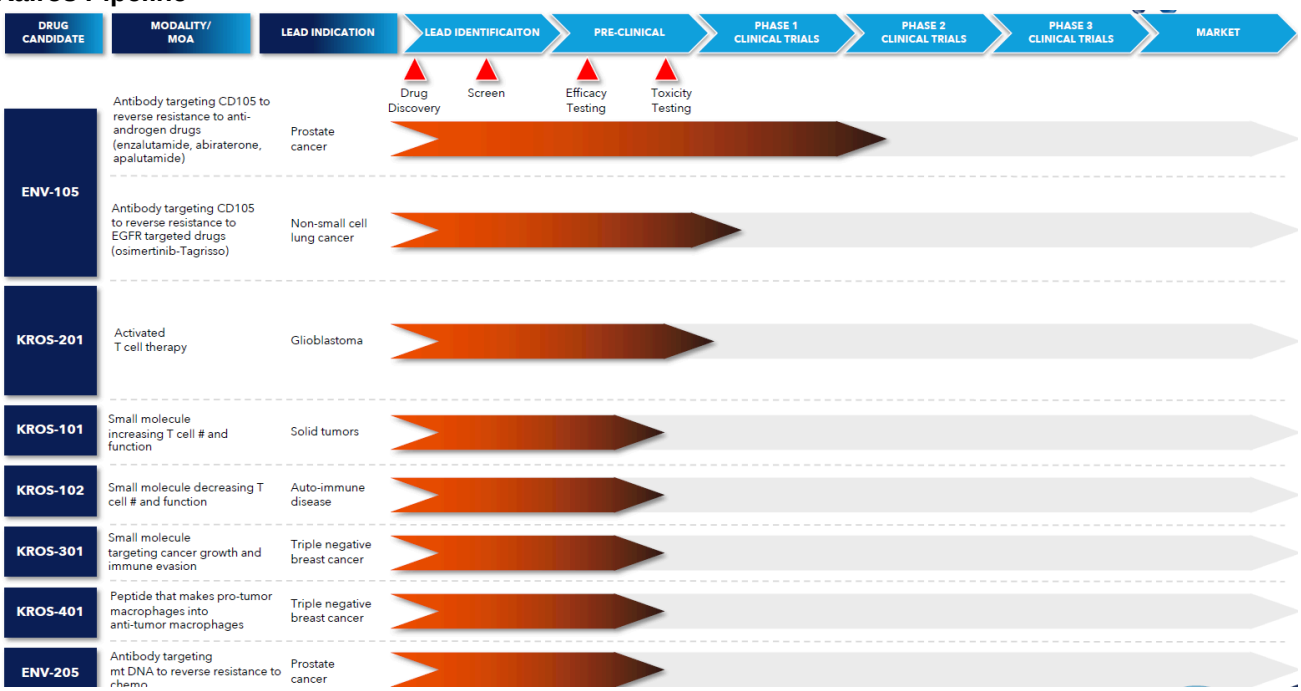
In May 2021, Tracon Pharmaceuticals (TCON; announced wind-down of operations in July 2024) entered into a license and supply agreement with Enviro Therapeutics. As part of the agreement, Tracon granted Enviro access to inactive IND filings for TRC105 in the U.S.; ownership of TRC105 stored vials of drug product manufactured to GMP standards; and assignment of Tracon's patent rights to its CD105 technologies. Further, Enviro paid Tracon an upfront fee of $100,000 and is obligated to make additional payments based on equity financings. The agreement also includes a 3% royalty on net sales and non-royalty payments for sublicensing fees. In exchange for its Enviro shares, Tracon received 280,000 shares of Kairos stock, equal to 1.41% of Kairos on a fully diluted and converted basis. The agreement grants exclusive licensing rights to multiple US and foreign patents. After its injectable PD-L1 inhibitor failed, Tracon ceased to be an operating company. Subsequent to the licensing agreement, in June 2021, Kairos acquired Enviro Therapeutics in a share exchange, through the issuance of 6,000,000 shares of Kairos stock, giving Enviro's shareholders ~20% voting power in Kairos. The acquisition of Enviro allowed the Kairos to incorporate Enviro's advanced pipeline of drug candidates, which includes ENV-105 (formerly known as TRC105), an antibody targeting CD105/Endoglin, currently in clinical development by Kairos for the treatment of prostate and lung cancer. To Kairos' benefit, Tracon invested millions of dollars in development of TRC105/ENV-105. The company also acquired Enviro's preclinical asset, ENV-205, an antibody targeting mitochondrial DNA for the treatment of chemotherapy resistance and cachexia.

On September 16, 2024, the company began trading on the Nasdaq Capital Market after a successful IPO, for total gross proceeds of $6.2 million. Company cash as of September 30, 2024 is $3.2 million. To this end, the company will need to raise additional capital to fund the clinical development and commercialization of its pipeline candidates.

The company boasts a broad pipeline of oncology assets and currently has two clinical stage programs: (1) the lead asset ENV-105 for the treatment of prostate cancer currently in Phase 2 studies; (2) ENV-105 currently in Phase 1 studies for the treatment of non-small cell lung cancer (NSCLC) and; (3) KROS-201 which recently cleared an IND for study in the treatment of glioblastoma (GBM). We currently only include ENV-105 in our valuation.

Kairos has an extensive IP portfolio of seven drug candidates, valid until 2040, which offers diversification and mitigates the overall exposure to many of the inherent risks of drug development. Key patents are licensed from Cedars-Sinai Medical Center, and Tracon Pharmaceuticals, Inc (with which Environ previously had licensing agreements). The science underlying the patents was developed at Cedars-Sinai Medical Center and was licensed from this institution.

Kairos Pipeline



Source: Company documents.

Candidate	Timeline	Milestone	Impact*
ENV-105	2Q25	Phase 2 Initial Safety/Interim Efficacy Data – Prostate Cancer	+++
	2H25	Phase 1 Initial Safety/Interim Efficacy Data – NSCLC	++

*HCW assessment of milestone's potential to represent a meaningful stock catalyst

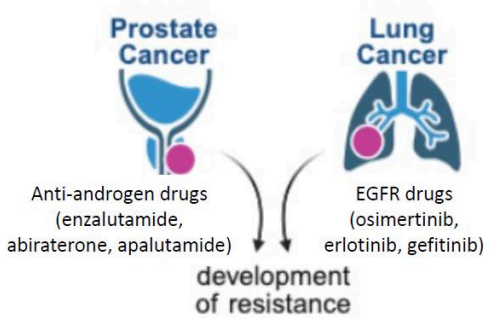
Source: HCW research.

We Are Bullish on the Shares of Kairos Based on the Following Five Factors:

1. **ENV-105: Overcoming Cancer Resistance Through Synthetic Lethality; Endoglin Could Be the Key**

Cancer immunotherapy market leaves much to be desired; endoglin can fill the gap. At its core, cancer is a disease of malignant cell transformation and proliferation, comprised of billions of growing cells. Despite the significant advances made with the advent of immunotherapy, our immune system seldom generates enough T cells to kill all cancer cells, often leading to low response rates and ultimately treatment resistance when the malignant clones successfully repopulate. Thus, a significant unmet need remains to target and reverse cancer cell resistance and overcome immune suppression. To combat this, Kairos has discovered a potential central mechanism utilized in multiple cancer types via the upregulation of CD105 (endoglin). Endoglin is a cell membrane glycoprotein mainly expressed on endothelial cells (ECs), and overexpressed on tumor-associated vascular endothelium, which functions as an accessory component of the transforming growth factor -beta receptor complex (TGFβ) and is involved in vascular development and remodeling. As patients are treated with drugs, the targeted cancer cells increase expression of cell surface endoglin for survival, rendering them resistant to therapeutic agents. Endoglin upregulation as a cancer drug resistance mechanism has been implicated across multiple tumor types and a variety of treatment modalities, including hormone and EGFR therapy, as well as in the resistance developed against radiation and chemotherapy. At the time of this report, Kairos is exploiting this mechanism for the treatment of prostate and non-small cell lung cancer (NSCLC), but there is potential for further indications including colon, breast and head and neck cancer tumors. As such, endoglin has emerged as a prime, druggable, vascular target for anti-angiogenetic cancer therapy.

Endoglin and the Development of Cancer Drug Resistance



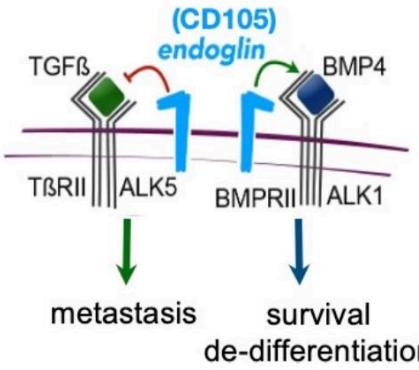
Source: Company materials

Endoglin mainly regulates malignant phenotypes of cancer cells by modulating TGFβ/BMP signaling. The TGFβ signaling pathway plays a crucial role in cellular proliferation, migration, differentiation, and apoptosis. The human TGFβ superfamily comprises TGFβs (1, 2, and 3), bone morphogenic proteins (BMPs), activins (A and B), and growth differentiation factors (GDFs). Seven TGFβ type-I receptors (TGFβRI: activin-like kinases (ALKs) and five TGFβ type-II receptors (TGFβRII) have been reported. In the canonical signaling pathway, after binding of the ligand to TGFβRII, it activates and phosphorylates TGFβRI, which subsequently transduces the signal by phosphorylating the downstream receptor-regulated SMAD molecules. The involvement of different TGFβRI (ALKs) can provoke the induction of different R-SMADs. Phosphorylated SMAD complexes are translocated to the nucleus, where

they modulate the transcription of specific target genes (Muñoz et al., *Int. Journal of Molecular Sciences* 2021).

Endoglin is found on proliferating endothelial cells in development and tumorigenesis (Fonsatti et al., *Oncogene*, 2003). It contains a long extracellular domain, a transmembrane domain, and a short intracellular tail that reflects its function as coreceptor for the TGFβ superfamily, since it does not initiate the signaling cascade but regulates it. In addition to two isoforms (L-endoglin and S-endoglin) that are anchored to the membrane and are produced through alternative splicing mechanisms, there is a soluble form that is produced through cutting the extracellular domain by matrix metalloproteinase (MMP) MMP-14 and MMP-12, in the case of inflammatory macrophages. Studies have shown that soluble endoglin functions in inhibiting TGFβ signaling and promoting bone morphogenic protein (BMP) signaling and regulating the balance between both signaling cascades across cellular types and contexts (illustrated in the schematic below).

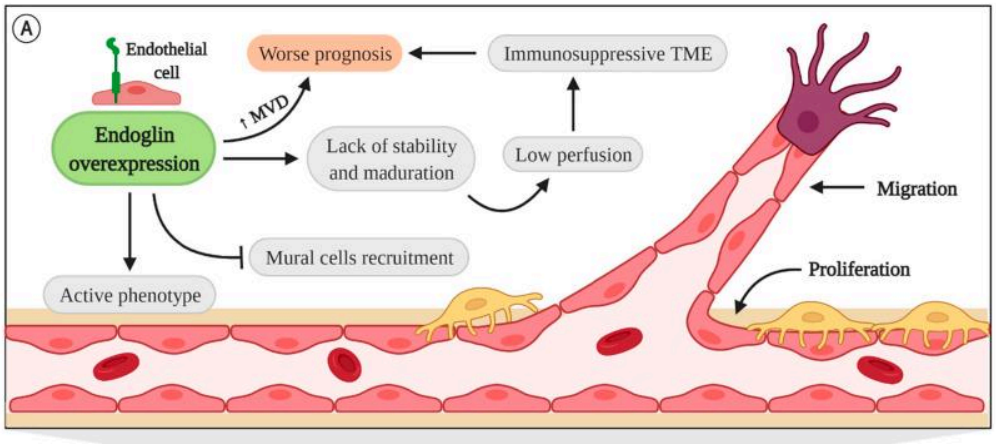
Endoglin Inhibits TGFβ and Promotes BMP Signaling



Source: Company materials

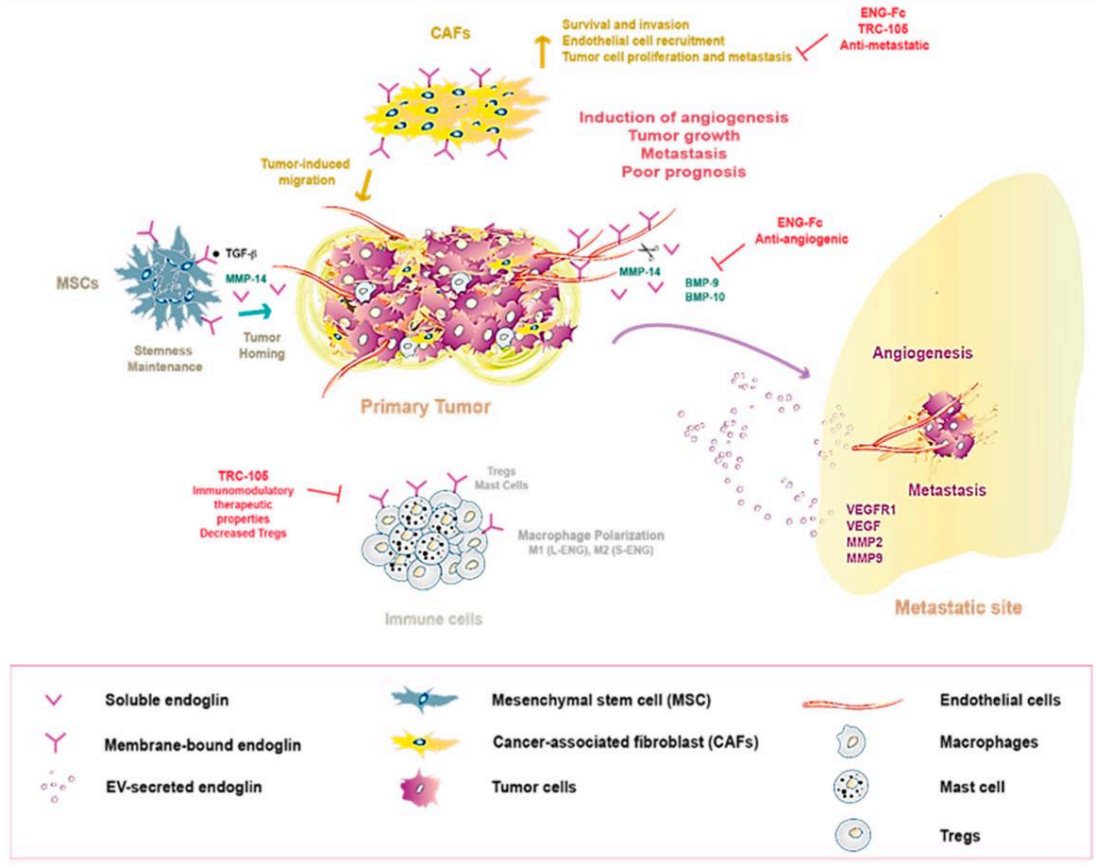
Endoglin is involved in the tumor's microenvironment, helping the cancer survive and resist treatment. In the context of cancer, TGFβ is a key immune-suppressive factor in the tumor microenvironment (TME) of most solid tumors, often limiting the efficacy of various immune-oncology therapies. Analysis of endoglin expression in tumors is already used in the clinic to study microvascular density and is associated with poor prognosis. The prognosis and response to immunotherapy depends largely on the composition of the TME. “Cold” tumors are rich in cells and molecules that inhibit the anti-tumor response and, therefore, are associated with a worse prognosis. In contrast, “hot” tumors are rich in anti-tumor cells and respond well to immunotherapy. A therapeutic strategy that has been shown to be useful for the conversion of cold tumors into hot tumors is vascular normalization. The establishment of one type of TME or another is highly dependent on angiogenesis, inflammation, and cancer-associated fibroblast (CAF) accumulation. As depicted in the figure below, endoglin is a protein involved in each of these three processes, actively regulating their behavior during tumorigenesis and making it a possible target for the conversion of cold tumors into hot tumors (Ollauri-Ibáñez et al., *Cancers* 2021).

Endoglin Is an Important Factor in the Generation of an Immunosuppressive TME.



Source: Ollauri-Ibáñez et al., Cancers 2021

Endoglin and ENV-105 (TRC105) Within the TME



Source: (Muñoz et al., Int Journal of Molecular Sciences 2021).

Turning back the hands of the cancer drug resistance clock with ENV-105. Studies have shown that endoglin is upregulated particularly in response to androgen-targeted therapy and EGFR inhibitors, which

are therapeutic strategies commonly used to treat prostate cancer and lung cancer, respectively (Madhav et al., *Oncogene* 2018; Wang et al., *PNAS* 2015). The goal of the ENV-105 program is reversing cancer drug resistance (i.e. those acquired through hormone therapy, radiation, I.O. etc.,) by exploiting synthetic lethality and enabling cancer drugs to last longer. A notable distinction we highlight, is that ENV-105 adds to the treatment armamentarium by reviving the previously used treatment (i.e. ADTs) without introducing a brand-new modality per se. And as a combination therapy, ENV-105 could be used to improve or extend the efficacy of ADT and Osimertinib in their respective indications, providing a unique market opportunity. Here, we see ENV-105 as being leveraged by big pharma to enhance their existing oncology pipelines. Currently, ENV-105 drug seeks to address unmet medical needs in large markets of prostate and lung cancers. For example, the global prostate cancer therapeutics market size is valued at $12.4 billion and at $4 billion for EGFR mutant NSCLC (*Global Market Insights 2024; PR Newswire 2023).*

As we discuss further below, the MoA for ENV-105 may address the resistance mechanism of tumor dormancy, because ENV-105 targets both the cancer cells as well as its supportive non-cancer environment. The advantage of targeting the unique environment supporting the tumor cells is that their capacity to adapt and evade therapy is significantly lower than that of the cancer itself. As such, ENV-105 is designed to address resistance to chemotherapy, radiation therapy, androgen targeted therapy, EGFR inhibitors, or checkpoint inhibition when given in combination. Interestingly, since the target of ENV-105, endoglin, is upregulated by the tumor and supporting cells in response to androgen targeted therapy and EGFR inhibitors as a proven mechanism of resistance, it stands to reason that the co-administration of ENV 105 can specifically target this mechanism of resistance.

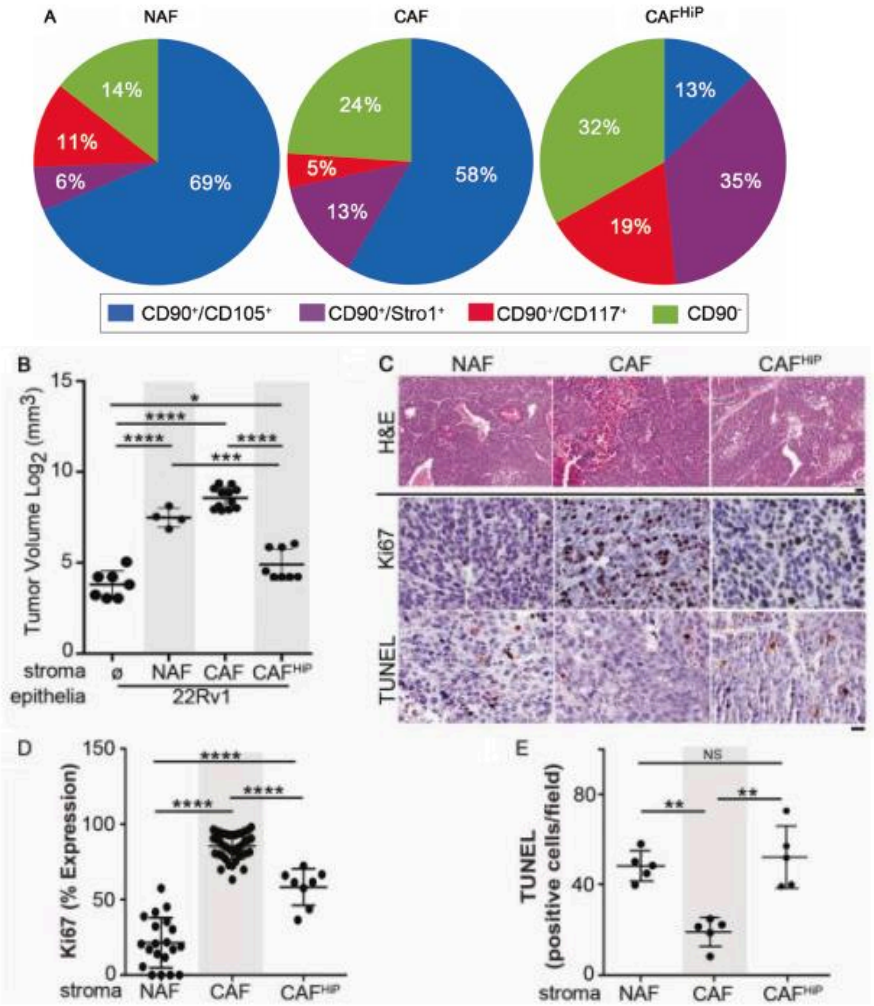
2. ENV-105 Can Reverse the Resistance in Prostate Cancer

Prostate cancer has a high unmet need. Prostate cancer is a heterogenous disease and the second highest cause of cancer mortality among men in the U.S. One of the key challenges in treating prostate cancer, especially with androgen-targeted therapies is the development of resistance, which has no curative approach. The prostate cancer incidence varies by age in U.S., but the total number of new cases across all ages is expected to be approximately 300,000 in 2024. The number of annual new cases is anticipated to rise year over year in the next decade. Steadily increasing estimates reflects the increased adoption and application of prostate-specific antigen (PSA) screening. The PSA test measures the amount of prostate-specific antigen in the blood, a protein produced by the prostate gland. PSA have tests has improved screening and early detection of the cancer. The PSA test is also used to monitor the progression of prostate cancer, and the rise in PSA levels is considered a marker of disease progression/reoccurrence. Upon initial diagnosis, treatment for prostate cancers includes: 1) surgery, 2) hormone therapy (also known as androgen deprivation therapy; ADT), and/or 3) chemotherapy. When prostate cancer is no longer responsive to hormone therapy, it is called castration-resistant prostate cancer (CRPC). CRPC incidence is approximately 10–20% of all prostate cancers within five years of diagnosis. Once CRPC spreads to other tissues and/or organs it is considered metastatic CRPC (mCRPC). The modest and unpredictable responses to current therapies, in tandem with high incidence of resistance, leaves the mCRPC space with a large treatable population and significant unmet clinical need. There is significant need in the space for novel and effective therapies that could innovate and improve upon current SoC practices (NIH Statistics; Scher HI et al., *PLoS One*, 2015; Beer TM et al., *NEJM*, 2014; Flaig TW et al., *JAMA Oncology*, 2017).

Stromal heterogeneity dictates prostate tumor progression. Regarding the heterogeneity of prostate cancer, previous studies have implicated TGFβ signaling in fibroblasts as a determinant for prostate epithelial plasticity. From the early steps of prostate cancer pathogenesis, the associated stromal fibroblastic cells begin to co-evolve with cancer progression and are predictive of recurrent disease and survival. The tumor-inductive properties of CAFs are such that they could convert non-tumorigenic epithelia to tumors and not simply based on proximity to cancer epithelia. Additionally, prostatic CAF are attributed

to tumor progression and therapeutic resistance to ADT. Endoglin has been identified in both normal-associated fibroblasts (NAFs) and CAFs, and its expression is diminished in high passage CAFs cell lines, as it well established that routine culturing of primary prostate CAF can lead to its loss of tumor-promoting potential. Kairos CSO Dr. Bhowmick and colleagues have done extensive work successfully demonstrating that endoglin positive CAFs are critical mediators of prostatic tumor epithelial differentiation and castrate resistance in a paracrine manner. Specifically, their work has shown that, when comparing the stromal makeup of primary CAF cultures generated from prostatectomy tissues, the most abundant fibroblast population within the NAF and CAF groups were CD90 (a marker of a pro-inflammatory state) and CD105/endoglin, compared to the CAF^{HiP} group (panel A, figure below). Further experiments build upon these findings and shows that in xenografts with the human prostate carcinoma epithelial cell line (22Rc1), tissues recombinant grafts using CD105+ CAFs resulted in significant tumor volumes with a distinct growth advantage compared to tissue recombinants using prostate epithelia alone, NAFs or CAF^{HiP}. CD105+ CAF-associated tumors were also found to have significantly greater Ki67-expressing epithelia (increased proliferation) and reduced TUNEL staining (reduced cell death), compared to NAF- or CAF^{HiP}-associated tumors.

Endoglin is Highly Expressed in CAFs

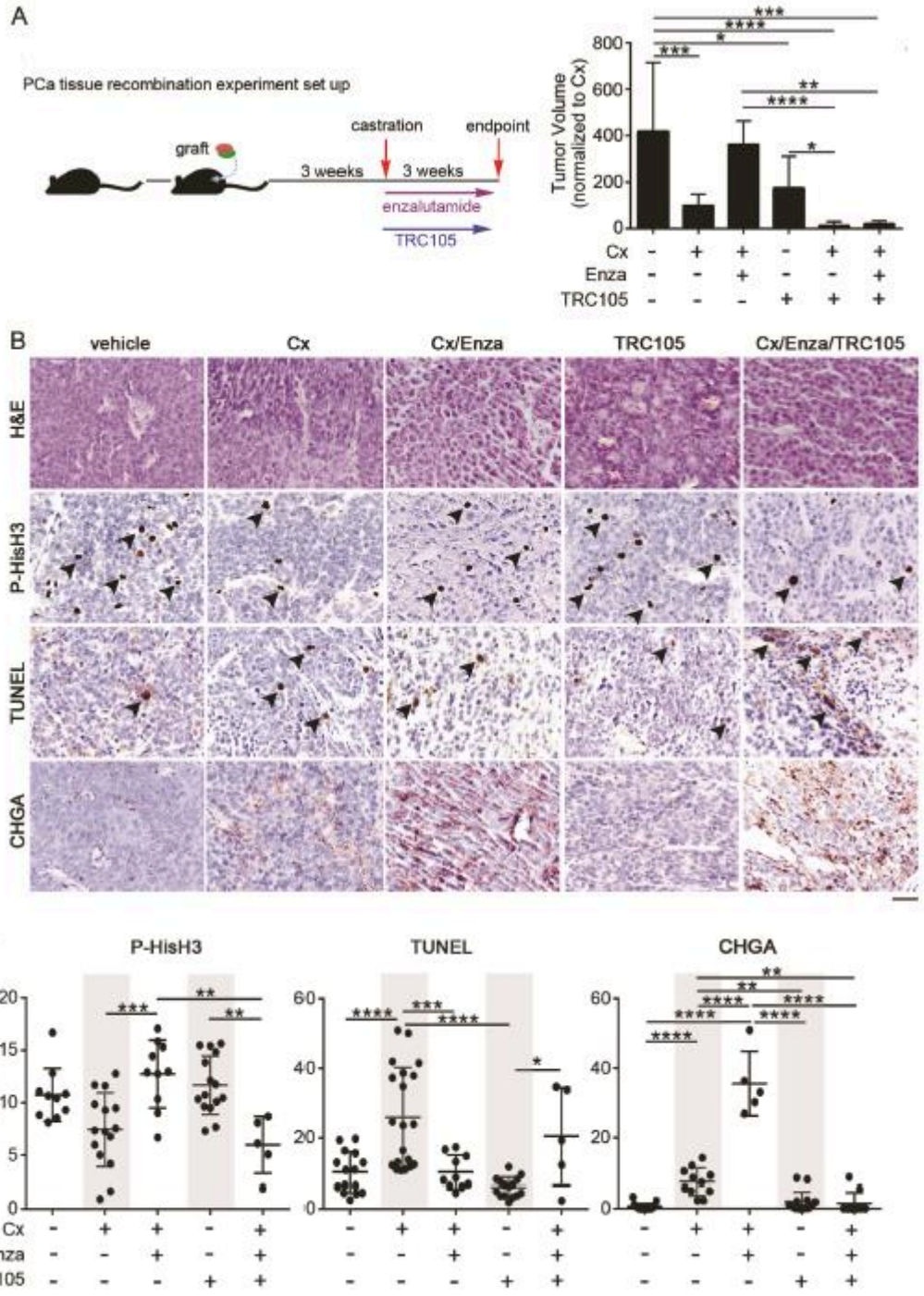


Source: Kato et al., Oncogene 2019

Hitting cancer where it hurts doubly; synthetic lethality MoA strives to reverse cancer drug resistance. Animal studies further confirmed that ADT resulted the expansion of the CD105+ CAF population. Interestingly, the combination of ADT with a neutralizing antibody against CD105/endoglin markedly reduced neuroendocrine differentiation and tumor size in a mouse model of therapy resistant disease. Stromal CD105 expression was shown to be associated with prostatic epithelial neuroendocrine differentiation both in patient tissues as well as patient-derived xenograft (PDX) models when administered with ADT. The data support the notion that targeting of both stromal and epithelial cell compartments with an endoglin targeting agent and ADT could provide a better therapeutic outcome for mCRPC patients. As such, study authors proposed a synthetic lethality hypothesis, and asked whether the inhibition of endoglin can "resensitize" or reverse castrate resistant prostate cancer to ADT, by simultaneously targeting the epithelia and its microenvironment with ADT and ENV105 (then known as TRC105 at the time of the studies). ENV 105, a partially humanized CD105 neutralizing antibody, targets both the cancer cells and the supportive tumor microenvironment, disrupting the mechanisms that allow the cancer to evade therapy. This dual targeting helps to prevent or overcome resistance mechanisms, such as tumor dormancy, which is a state where cancer cells remain inactive and resistant to conventional therapies.

In a novel synthetic lethality paradigm, the study authors found that simultaneously targeting the epithelia and its microenvironment with ADT and TRC105, respectively, reduced castrate-resistant tumor progression, in a model where either ADT or TRC105 alone had little effect (see figure below). The preclinical *in vivo* studies highlighted below utilized an orthotopic CRPC mouse model comprised of human CAF and a 22Rv1 (a human cancer cell line) (Kato et. al., *Oncogene* 2019). The tumors were allowed to expand for 3 weeks prior to castration and mice were then treated with enzalutamide (an ADT SoC), either with or without combination with TRC105 for 3 weeks to better mirror clinical conditions where secondary treatment after castration equivalent therapies failed. Study authors found that castrated mice had markedly reduced tumor volumes compared to control mice. In this CRPC mouse model, the castrated mice given enzalutamide had tumor volumes comparable to control intact mice and mice treated with TRC105 alone had tumors smaller than vehicle control ($p < 0.05$). To better compare to the real-life scenario of patients on enzalutamide being in a castrate state, the study authors evaluated the combination of castration with enzalutamide and compared the arising tumors following TRC105 treatment. Tumor size was significantly reduced following the addition of TRC105 when compared to either control mice or castrated-enzalutamide treated only mice ($p < 0.001$ and $p < 0.01$, respectively). Castrated mice treated with TRC105 exhibited the smallest tumor volume compared to control mice with a $p < 0.0001$. Notably, these minimal tumors were too small to section for reliable histologic analysis. Chromogranin A staining (CHGA), a marker of neuroendocrine differentiation associated with ADT, was significantly reduced by the added treatment with TRC105 in castrated mice (p value < 0.0001) along with a concomitant increase in cell death (TUNEL).

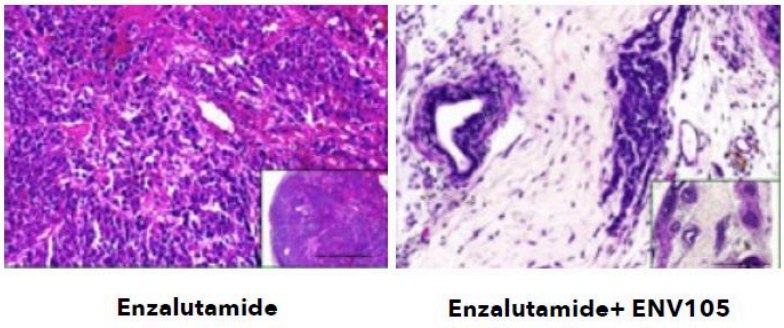
ENV105 (TRC105) Sensitizes Prostate Cancer Cell to ADT *In Vivo*



Source: Kato et al., Oncogene 2019

Further highlighted in the figure below, when comparing growing cancer cells treated with enzalutamide alone after treatment resistance has developed (left), compared to the cells that have been given the combination of enzalutamide + ENV105 (right), we can see a dramatic reduction in cancer cell proliferation in those cells given the combination treatment. These findings suggest that ENV-105 allows enzalutamide to work again to kill prostate cancer cells, effectively reversing the initially acquired resistance.

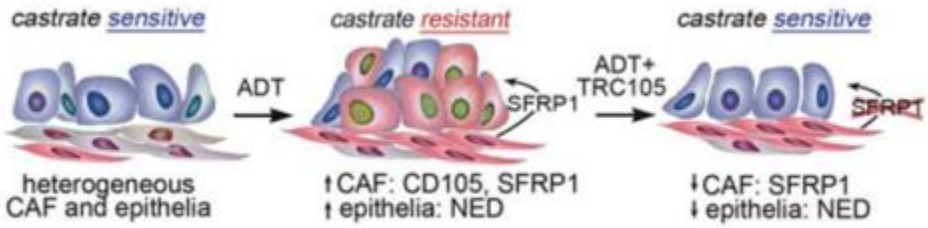
ENV105 Reverses Resistance to Enzalutamide



Source: Company materials

Additional work showed that a key CD105-asosciated mediator of tumorgenicity in the CAF population was, secreted frizzled-related protein 1 (SFRP1), associated with epithelial branching morphogenesis in the prostate, induction of neuroendocrine features in prostate cancer cells, and tumor progression. The identification of this population, a stromal CD105-expressing population in CAFs that can mediate neuroendocrine differentiation and subsequent CRPC (illustrated in figure below), is a crucial mechanistic understanding, as it is known that despite promising initial efficacy with ADT, many patients continue to progress towards CRPC, with the acquisition of neuroendocrine features by the cancer epithelia. Kato and colleagues identified that CD105/BMP signaling is upregulated in response to ADT using mouse models. They further found that stromal CD105 expression was associated with prostatic epithelial neuroendocrine differentiation in patient tissues. Adding to this mechanistic understanding, the study authors also identified that CD105 blocks AR-V7 cleavage, which is a route of resistance. Taken together with *in vivo* studies, we can see a therapeutic strategy whereby combining ADT with ENV105 to reduce neuroendocrine differentiation and subsequent tumor size could be employed in CRPC.

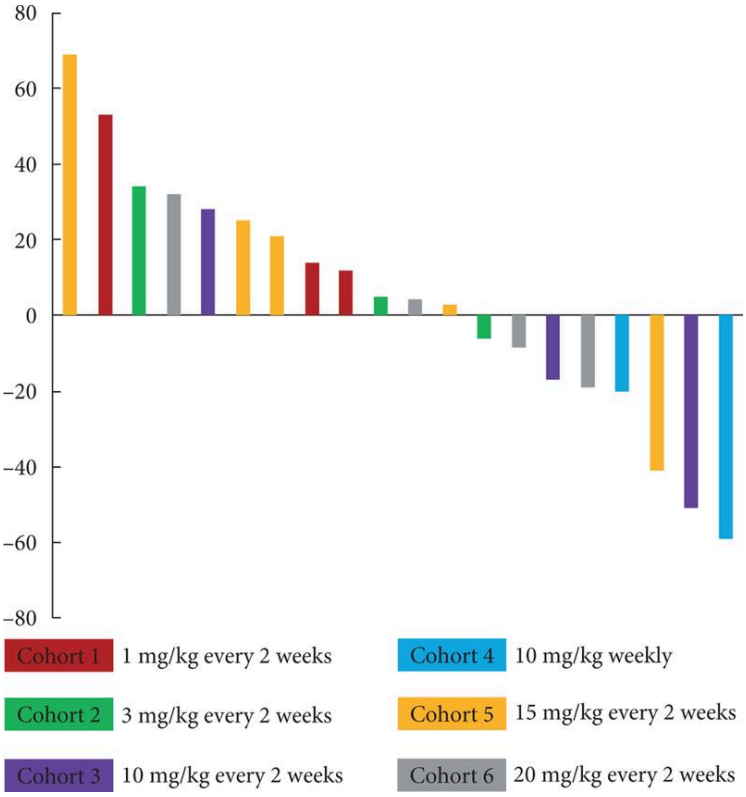
Endoglin and CAFs in Prostate Cancer Pathogenesis



Source: Kato et al., Oncogene 2019

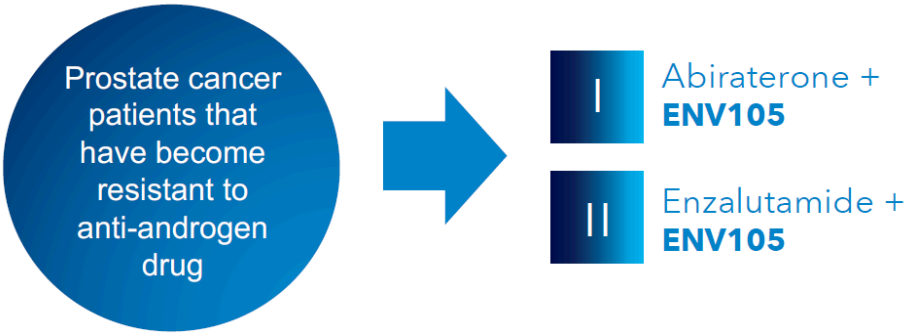
ENV-105 and prostate cancer; reversing the resistance; completed Phase 1 study shows encouraging early profile; Phase 2 ongoing. Backed by a strong preclinical data package, ENV-105 first entered the clinic as TRC105 when Tracon still owned the asset. In the Phase 1 open-label study, mCRPC patients received escalating doses of TRC105 using a standard 3+3 study design *(Karzai et al., BJU International 2014).* A total of 20 patients were enrolled, with the top dose of 20 mg/kg being delivered every 2 weeks. TRC105 had a favorable safety profile, and per study authors, common AEs including infusion-related reactions (90%), low grade headache (67%), anemia (48%), epistaxis (43%) and fever (43%). Ten patients had stable disease on study and eight patients had declines in PSA, two of which were over 50% (see figure below).

Percent Change in PSA Level From Baseline – Phase 1 Study



Source: (Karzai et al., BJU International 2014).

Following these initial results, a small Phase 2 IST study of ENV-105 in heavily pre-treated mCRPC was initiated at Cedars-Sinai Medical Center in 2018 (still under Tracon's license). As outlined below, the study tested whether ENV-105 could make prostate anti-androgen drugs work again when the cancer became resistant to either abiraterone or enzalutamide (two forms of hormone therapy that blocks the androgen receptor and its target ligand, testosterone, respectively). These two agents are considered standard of care for nearly all recurrent prostate cancer patients.



Source: Company materials

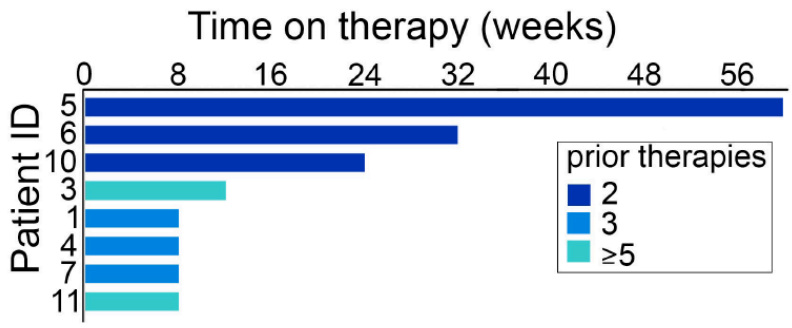
The primary endpoint of the study was change in PSA and radiographic response in patients at two months. A clinical benefit rate of 62% was observed. The trial enrolled 11 patients of which 9 were evaluable. In addition, ENV-105 was also safe and well-tolerated, with no grade 3-4 toxicities observed with the

combination. This IST trial closed to accrual prior to its planned enrollment of 40 patients due to limitations of the drug supply from the manufacturer. The drug supply has since been expanded and obtained by Kairos Pharma.

The trial accrued patients who were resistant to the very ADT (enzalutamide or abiraterone) that was given in the trial, in addition to ENV-105, in order to evaluate the ability of ENV-105 to reverse the acquired resistance. Importantly, ENV-105 administration alone showed no clinical benefit, based on pre-clinical findings conducted by Kairos, and previous clinical findings (performed by the National Cancer Institute). However, two agents that apparently have no clinical effect, when combined result in halting tumor progression in most patients. The finding is supported by numerous publications reporting on studies that demonstrated hormone therapy resistance develops through the induction of CD105, the target of ENV-105.

In addition, all the patients participating in the trial were not only resistant to the two hormone therapy agents but also resistant to at least one other intervention after surgical or radiation progression. Some patients failed to respond to as many as five other drugs. The responders to the combination therapy were patients who, at that point, had exceedingly few other options for survival. Highlighted in the graph below, the time on combination therapy is indicated with relation to the number of clinical interventions prior to accrual to the Phase 2 clinical trial for the individual patients.

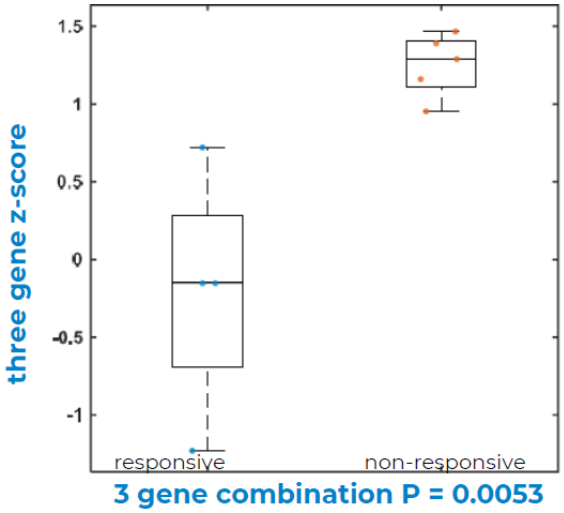
Phase 2 Subjects Had Multiple Prior Clinical Interventions



Source: Company materials

Concurrent to the Phase 2 trial, a three-gene panel was identified to serve as a companion biomarker for patient selection. The panel was used to distinguish potential drug responsive and non-responsive patients, prior to therapy, based on the expression level of three genes. Currently under co-development with the Kairos subsidiary, Enviro (acquired in 2021), we see the companion biomarker test as a significant value-add to the ENV-105 program as a means to further ensure successful clinical development and outcomes through to the NDA and FDA approval process.

Biomarker Testing: Predicting Patient Responsiveness Prior to Therapy

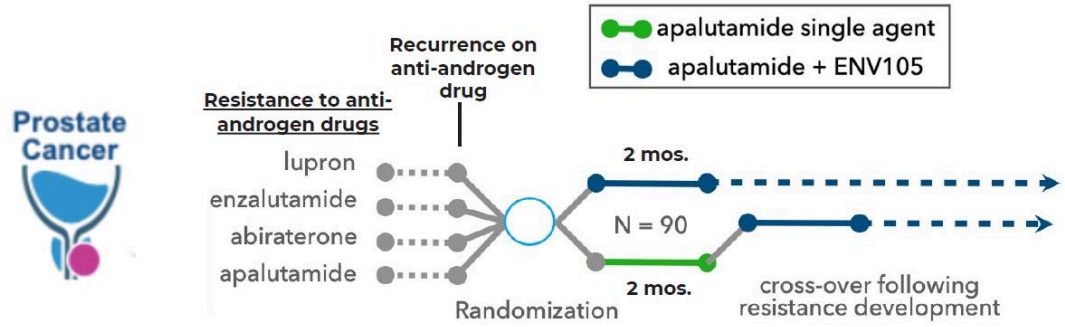


Source: Company materials

Randomized Phase 2 study underway; Interim Data Expected 1H25. The biomarker test development is further supported by a $3.2 million NIH grant to Kairos CSO, Dr. Bhowmick, which will be used and verified in the present, ongoing Phase 2 trial of ENV-105 in prostate cancer at Cedars-Sinai. The ENV-105 Phase 2 multi-center trial in prostate cancer will be randomized with and without ENV-105 in patients treated with apalutamide (Erleada) (JNJ; not rated). Outlined below, enrolled patients will have failed at least one prior line of ADT therapy. The study is targeting enrollment of 90 patients, to be randomized and given apalutamide as single agent or in combination with ENV-105 for 2 months (the single agent arm can cross-over following resistance development). The primary endpoint of the study is progression free survival (PFS), and the secondary endpoint is companion biomarker confirmation. Per management, the benchmark for response is if PFS in the combination arm can go beyond 4 months (as 2L or 3L mCRPC typically become resistant ~2months) in 50% of patients. At 4 months, it is expected that patients on apalutamide would demonstrate tumor progression. PFS is radiographic imaging and PSA (prostate specific antigen in the blood). Both are utilized since as prostate tumors become more aggressive (gain small cell characteristics), they can lose the ability to express PSA. This is by RECIST 1.1 and Prostate Cancer Working Group 3 (PCWG3)57 criteria. The bar for success for this trial for 2L therapy is stated at 50% patients having PFS over 4 months in the group receiving apalutamide and ENV 105.

The study began enrolling patients in September 2023 and management has guided that drug supply will not be a concern or limitation in this ongoing study. The study is currently enrolling patients Cedar-Sinai Medical Center, City of Hope Cancer Center, and Hunstman Cancer Institute. The study has now accrued all the patients required for a safety readout (n=10). The second part of the study, which randomizes patients to receive either apalutamide alone or in combination with ENV105 is ongoing. The company expects to announce the safety and efficacy data readout from the safety arm of the trial om 1H25.

Current Randomized Phase 2 Trial: Apalutamide +/- ENV105



Source: Company materials

When considering the competitive landscape, and other therapeutics in development addressing resistance mechanisms that could be utilized after ADT, we see a viable opportunity for ENV105. Current comps in the space include Janux Therapeutics (JANX; Buy; Ramakanth) and Vir Biotechnology (VIR; Buy; Trucchio) which are both developing T cell engagers for use in mCRC after ADT. However, to date, immune therapy has not provided much benefit thus far for prostate cancer patients, as it is among the tumor types though to be "immune cold." The bispecific antibodies in use unfortunately have not been able to recruit enough T cells, as of yet. However, there may be a tumor metastatic site that would makes these more favorable – for example with the recent, early Phase 1 Janux data for JANX007. Further, Novartis' Pluvicot (NVS; not rated), which recently surpassed $1 billion in sales in 2023, for mCRPC post-ADT, the objective response rate is 51% and toxicity is substantial (52.7% grade >3 toxicity). Since ENV105 is given with standard of care hormone therapy without added toxicity, we expect market penetrance to be high. As men age the toxicity profile can be a significant determining factor. As such, even though chemotherapy has been the standard of care for some time for those failing hormone therapy, many patients opt out voluntarily.

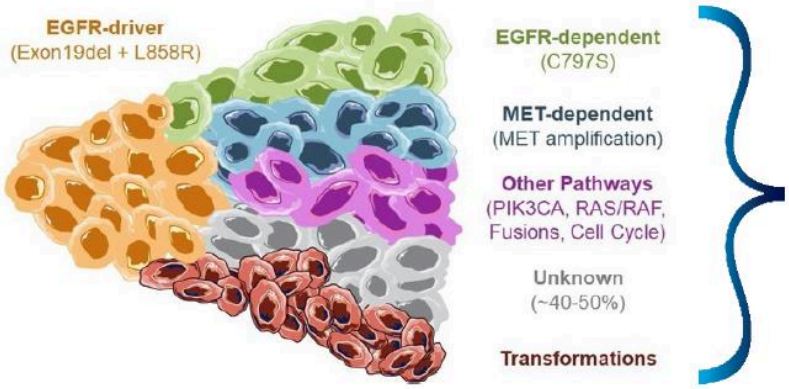
3. ENV-105 extends its reach to EGFR- treatment resistant NSCLC.

ENV-105 extends its reach to EGFR- treatment resistant NSCLC. The second indication currently being evaluated with ENV-105 NSCLC. Lung cancer is the third most common cancer and the leading cause of cancer death in the U.S. In the U.S., lung cancer occurs in approximately 230,000 patients and causes over 130,000 deaths annually. NSCLC accounts for ~85% of primary lung cancers and 70% of NSCLC patients have advanced disease at clinical presentation (stage III/IV). This may reflect the aggressive nature of the disease and the frequent absence of symptoms until locally advanced or metastatic disease is present. High-risk patients may be diagnosed while asymptomatic through screening with low-dose computed tomography. There is high unmet medical need with median survival for all types of NSCLC being 16 months. Overall five-year survival rates have improved incrementally from 14.7% to 31.1% (Abedi et al., *J Prev Med Public Health* 2019). Targeted treatment results in responses that are better than those achieved with standard chemotherapy for certain subtypes of NSCLC, including those with driver mutations such as epidermal growth factor receptor (EGFR), which is commonly observed in NSCLC, particularly in tumors of adenocarcinoma (ADC) histology. *EGFR* mutations account for approximately 15% of all NSCLC cases (Midha et al., *Am J Cancer Res* 2015). In 2023 alone, 45,000 EGFR-driven NSCLC cases were diagnosed.

EGFR is a membrane-bound receptor tyrosine kinase of the ErbB family. Activation causes downstream effects via several signaling pathways including RAS/MAPK, JAK/STAT, and PI3K/AKT/mTOR. Downstream effects include proliferation, migration, and survival. Activation of EGFR, therefore, is

considered an oncogenic driver. EGFR mutants can be categorized as either activating mutations or resistance mutations. EGFR-mutant NSCLC patients are typically treated with tyrosine kinase inhibitors (TKIs), which specifically target *EGFR* oncogenes (Midha et al., *Am J Cancer Res* 2015). Tagrisso (Osimertinib; AstraZeneca; AZN; Not Rated), a third generation TKI, has emerged as the standard of care for patients diagnosed with EGFR driven NSCLC. However, many patients on therapy develop resistance via acquired mutations, which can occur through bypass tracts such at *MET* amplification, or through on-target mutations to first-generation EGFR-TKI such as T790M or to third-generation EGFR-TKI (i.e. osimertinib) such as C797S (as shown in schematic below).

Treatment Resistant Remains a Challenge in Treating EGFRmut NSCLC



Source: Company materials

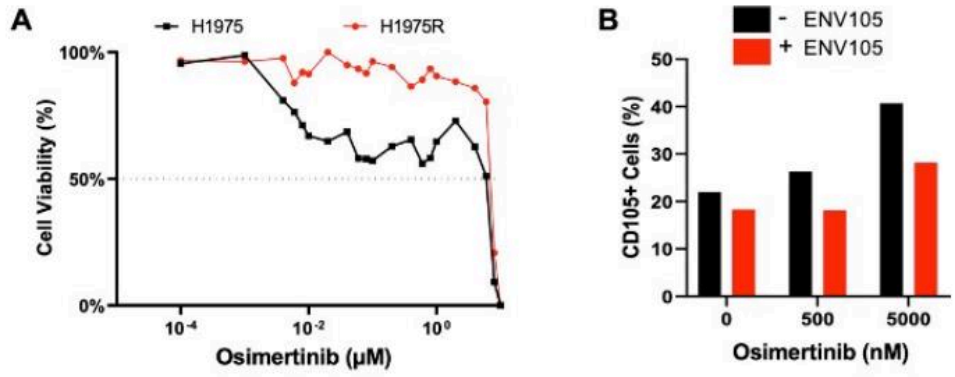
The success of osimertinib stems from it being mechanistically unique from first and second-generation TKIs with additional activity against T790M mutants in addition to activity against canonical EGFR-sensitizing mutations (exon 19 deletion and L858R) while sparing wild-type EGFR more than previous generation EGFR-TKIs (Finlay et al., *J Med Chem* 2014). We note that as compared with standard chemotherapy in NSCLC patients with acquired resistance to 1st-gen EGFR TKIs (T790M-driven)—osimertinib reports an ORR of 71% compared to 31% (chemo alone) with a PFS of 10.1 months vs 4.4 months. This study also showed that in patients with CNS metastases the median PFS was 8.5 months for osimertinib compared to 4.2 months for chemotherapy. Additionally, the pivotal FLAURA study reported that when osimertinib was compared with gefitinib or erlotinib in 1L patients with advanced EGFR-mutant NSCLC, it achieved an 18.9- month PFS compared to 10.2 months, with a lower incidence of CNS progression (6% vs 15%) and increased OS to 38.6 months from 31.8 months (Cooper et al., *Nat Rev.* 2022).

Novel combinations with osimertinib could crack the resistance in EGFR-driven NSCLC. Regardless of strong efficacy signals, similar to earlier generation TKIs, the problem of eventual progression and development of eventual resistance mechanisms arising from targeted therapy exists with third-generation TKIs including osimertinib, rendering majority of patients to partial responses and refractive disease with limited treatment options. Taken together, there remains a critical need for novel approaches/combinations with osimertinib for next generation treatment options to treat EGFR-driven NSCLC.

ENV-105 could re-sensitize EGFRmut, osimertinib refractory NSCLC. Bhowmick and colleagues identified a mechanism whereby ENV-105 can re-sensitize osimertinib resistant EGFRmut NSCLC, by demonstrating that osimertinib resistance is dependent on CD105/endoglin. Through a protein expression

analysis of 76 NSCLC patients, study authors found that EGFR expression was inversely correlated with endoglin membrane expression. Elevation of cell surface endoglin by osimertinib was furthered by EGFR knockdown in *in vitro* studies using NSCLC cell lines with EGFR activating mutations. Shown below, EGFR mutant NSCLC cells (H1975) made resistant to osimertinib (H1975R) resulted in elevated cell surface CD105 expression by FACS analysis. The co-administration of ENV-105 downregulated CD105 expression.

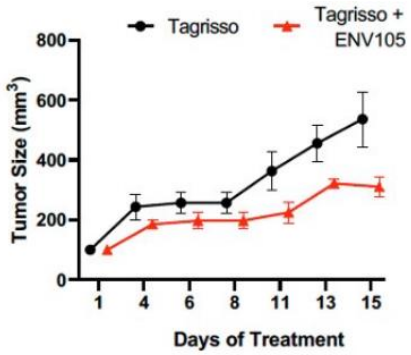
Osimertinib Resistant Cell Lines Sensitive to the Combo of ENV105 + Osimertinib



Source: Company materials

NSCLC tumor cells resistant to osimertinib were xenografted (figure below). Osimertinib (Tagrisso) treatment resulted in tumor expansion, whereas the combination with ENV105 significantly diminished tumor expansion (p value < 0.0001).

Combo of ENV105 + Osimertinib Significantly Reduces Tumor Expansion *In Vivo*



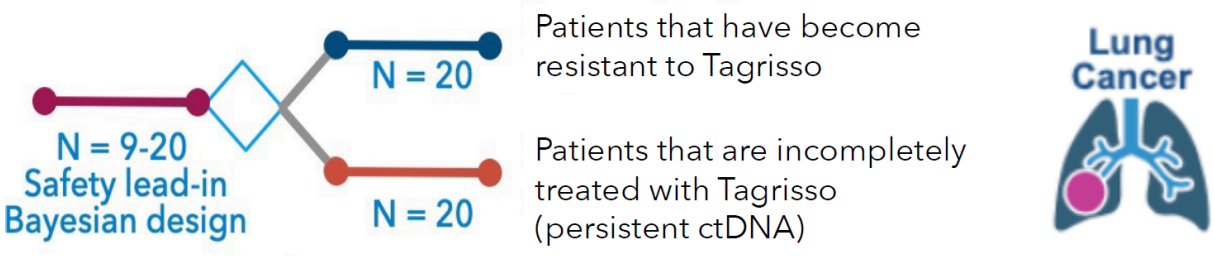
Source: Company materials

Taken together, these preclinical findings suggest that inhibition of CD105/endoglin with ENV-105 can overcome resistance to osimertinib and inhibit NSCLC tumor progression. These provide a first-in-class preclinical foundation for a novel synthetic lethality treatment strategy resulting from the observation of global changes in EGFR-antagonist resistance as opposed to individual mutations identified in tumor subpopulations *(Thiruvalluvan M et al. Cancer Res 15 March 2024; 84 (6_Supplement): 4759).*

With a solid preclinical foundation, ENV-105 has entered the clinic in a Phase 1 study evaluating ENV-105 in EGFRmut NSCLC patients who have developed resistance to prior treatment with osimertinib (study

design outlined below). The study is looking to recruit 55-60 patients total in the Phase 1a (~10-15 patients) and Phase 1b (40 patients) To date, 6 of the Phase 1a patients have been accrued thus far. The reason the Phase 1a is approximately 10 patents is because it is a Bayesian design (or adaptive design) that is a dose finding strategy. The Phase 1b has two arms with patients that have resistance to Tagrisso or partial Tagrisso sensitivity, where ENV105 will be evaluated for its ability to improve both patient responses. The partial response category makes up about 80% of all patients on Tagrisso today. The study primary endpoint is to determine the safety and effective dose of ENV-105 in patients with EGFRmut lung cancer. The secondary endpoint is to identify biomarkers for patients most responsive to ENV-105. Five clinical sites are currently open and enrolling patients. The first patient was recently dosed and the company expects to report initial safety and interim efficacy data from the Phase 1a by YE25. The company is also looking to open another two sites currently, however they will likely come online for Phase 1b portion of the trial. In terms of benchmarking for response, for EGFR-driven lung cancer, the criteria is EGFR mutation detection circulating tumor DNA (ctDNA) in blood. So, as long as there are no new mutations that appear in sequential blood draws the patients is deemed to be responsive.

Phase 1 Trial Design for EGFR-Driven Lung Cancer: Osimertinib + ENV105

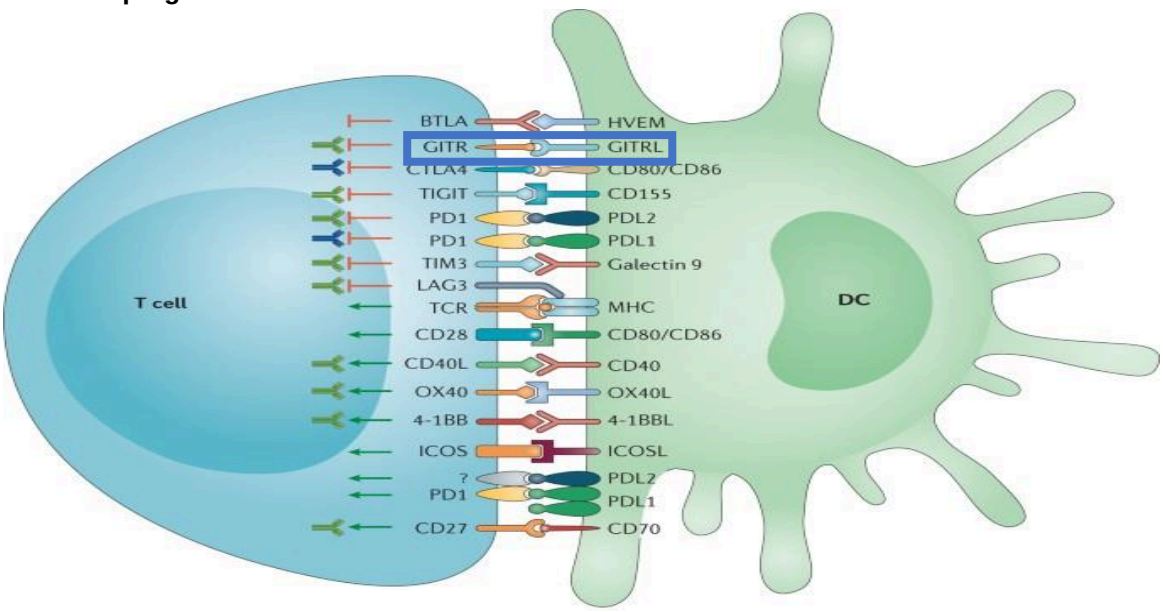


Source: Company materials

4. **KROS-101 and KROS-102 hitting GITR from both ends and across indications.**

GITR: an immune activator that turbo charges immune cells for a broad and potent anti-cancer response. The glucocorticoid-Induced TNFR-Related (GITR) protein is a cell surface immune coreceptor belonging to the Tumor Necrosis Factor Receptor Superfamily (TNFRSF), which includes other immune costimulatory receptors such as 4-1BB/CD137 and OX40/CD134. GITR is an activating receptor that stimulates both acquired and innate immunity and acts a checkpoint central to control the numbers of T cells of the immune system (Davar et al., *Clinical Cancer Research* 2022). It is expressed in several cells and tissue types, including T and Natural Killer (NK) cells and is activated by its ligand, GITR. GITRL is mainly expressed on Antigen Presenting Cells (APCs) and endothelial cells (see schematic below). The effects of stimulation through GITR are generally thought to be caused by attenuation of the effector activity of immunosuppressive CD4+CD25+ regulatory T (TReg) cells. The GITR/GITRL system participates in the development of autoimmune/inflammatory responses and graft vs. host disease and potentiates response to infection and tumors. These effects are due to several concurrent mechanisms including co-activation of effector T-cells, inhibition of Treg cells, NK-cell co-activation, activation of macrophages, modulation of DC function and regulation of the extravasation process (Nocentini and Riccardi *Adv Exp Med Biol* 2009).

GITR is Upregulated on Activated T-Cells



Source: Company materials

GITR antibody in cancer: finally ready for prime time? GITR agonistic antibodies are expected to increase the antitumor response mainly by reducing the effect of Foxp3+ Treg cells. The GITR-GITRL interaction facilitates receptor trimerization, which is vital for downstream signaling and T cell activation. However, to date, there has been a discordance between preclinical data and observed clinical efficacy.

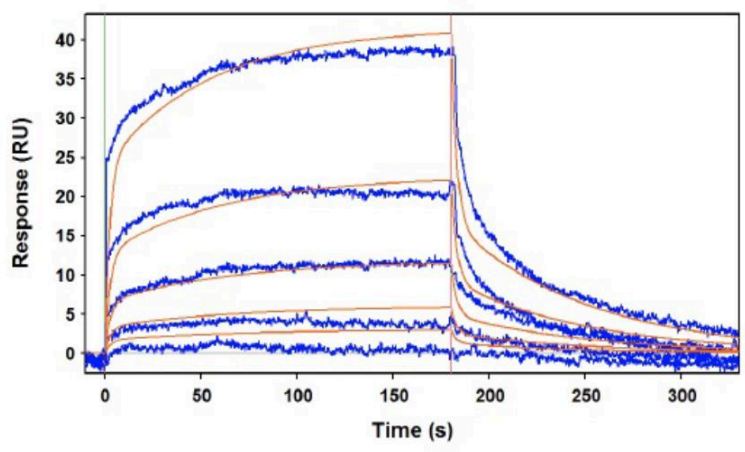
While murine studies have previously demonstrated effective T cell proliferation and Treg suppression via trimerization, clinical trials using GITR agonist antibodies have shown limited efficacy, likely due to suboptimal trimerization of human GITRL, with one example observed with Leap Therapeutics' TRX-518 (LPTX; Neutral; Ramakanth). TRX-518 was developed as a GITR agonist that showed acceptable pharmacodynamic activity by depleting Tregs in preclinical models, however, saw limited clinical activity demonstrated in patients with advanced solid tumors, along with signs of gastritis (Davar et al., *Clin Cancer Res.* 2022). Together, these lackluster findings from competitor assets led to reduced investor interest in GITR development as a cancer therapeutic. To address these concerns, the Kairos team identified that soluble human GITRL exists in an equilibrium between dimers and trimers and has leveraged this finding to develop KROS-101. KROS-101, currently in preclinical development, is a novel, orally available small molecule agonist designed to stabilize GITRL trimerization and enhance GITR signaling. In the context of cancer treatment, it is designed to deplete Tregs and activate effector T cells to augment the antitumor immune response for the treatment of patients with cancer.

KROS-101 and checkpoint inhibitors could tackle solid tumors together. GITR is a powerful checkpoint that suppresses the immune response against cancer. This checkpoint is a central switch that promotes "killer" effector T cell functions and hampers inhibitory Treg functions. Due to its central role in regulating Treg, GITR receptor complex is considered an optimal therapeutic target for treating cancer. Enter KROS-101, which is being developed as a systemic immune modulator to address immunosuppressive activity of solid cancers. The discovery of KROS-101 was the culmination of extensive structural biology work, based on exclusive proprietary 3D crystallography first used to model GITR ligand by Kairos' scientists.

When thinking of how KROS-101 could be added to the current cancer treatment landscape, there could be a viable opportunity in combination with checkpoint inhibitors. KROS-101 may be the optimal complement to add to current checkpoint inhibitors as it shows a dose dependent effective response in increasing the immune response in preclinical studies. As a competitive antagonist, KROS-101 could be dosed to avoid the typical common side effects of checkpoint inhibitors. A GITR targeting small molecule has the potential to be a significant improvement over existing antibody treatments that have been tested in clinical trials. When GITRL binds to the GITR on the surface of Treg cells, the suppressive activity of Treg cells against effector T cells is reduced. While on the effector T cell, GITR/GITRL binding induces the proliferation of effector T cells. This receptor is central to the regulation of the immune system. Whereas previous competitor therapeutics targeting GITR were antibodies that bind the receptor, the KROS-101 small molecule drug fits into the GITR ligand stabilizing the three-pronged trimer structure. This structure enables the amplification of the GITR receptor trimer, leading to physiologic signaling for T cell proliferation. This robust physiologic signal can lead to exponential signaling of T cells to proliferate against cancer cells. In addition, the small molecule half-life enables reversibility, allows for fine tuning to limit side effects. Having both agonist and antagonist molecules can reverse potential untoward effects observed with previous iterations of competitor GITR-based assets.

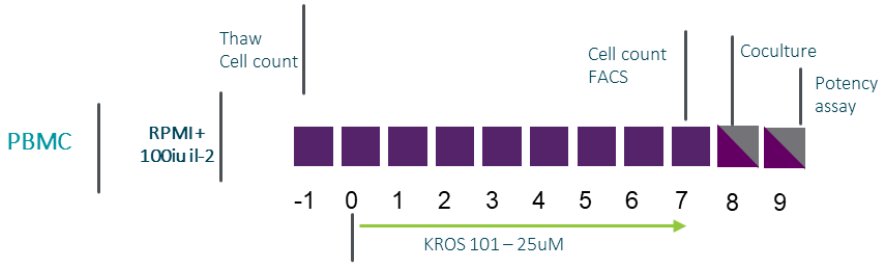
Preclinical findings support clinical development of KROS-101. As we highlight below, Kairos has assembled a strong preclinical data package demonstrating the potential of KROS-101. In brief, KROS-101 demonstrated high-affinity binding to human GITRL in surface plasmon resonance assays and significantly enhanced CD3+ T cell proliferation *in vitro*, expanding both CD4+ and CD8+ subsets while reducing Treg proliferation. KROS-101-treated T cells exhibited superior cytotoxicity against glioblastoma (GBM) cells and patient-derived glioma cancer stem cells (CSCs).

KROS-101 Binds to Human GITR Ligand With High Affinity



Source: Company materials

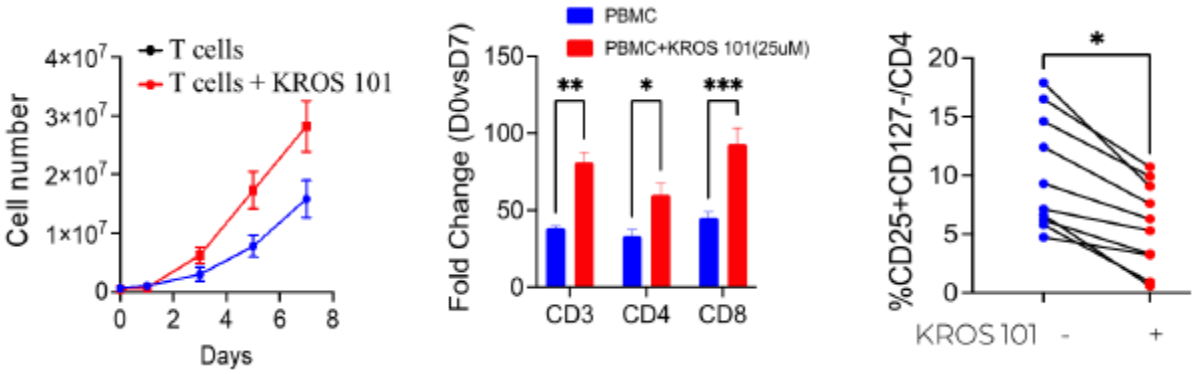
KROS-101 Boosts Effector T Cell Expansion and Reduces Treg Population



Source: Company materials

Following KROS-101 treatment there is an observed increase in proliferation of T cells (left panel), with quantification of CD3+, CD4+ and CD8+ T cell percentages, demonstrating a concomitant, significant increase in T cell expansion (middle). Quantification of the Treg population shows a significant reduction in Tregs in the presence of KROS-101 (right panel).

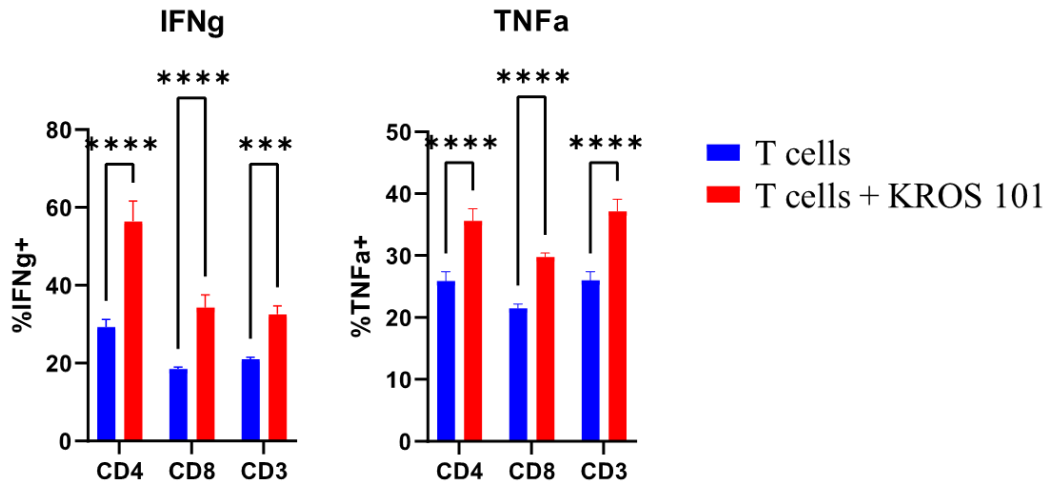
KROS-101 Boosts Effector T Cell Expansion and Reduces Treg Population



Source: Company materials

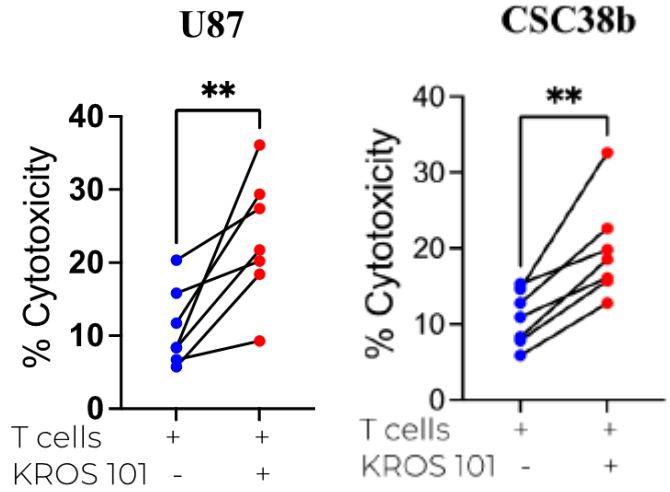
Quantification of IFN-γ (left) and TNF-α (right) production by CD3+, CD4+, and CD8+ T cells treated with KROS-101 (red bars), demonstrate significantly enhanced effector cytokine responses compared to untreated controls (blue bars).

KROS-101 Treated T Cells; Enhanced Effector and Effector Function Markers



The cytotoxicity assay below highlights the increased killing of glioblastoma (U87 cell ine) and glioma cancer stem cells (CSC38b) by KROS-101-treated T cells at a 10:1 effector-to-target (E:T) ratio.

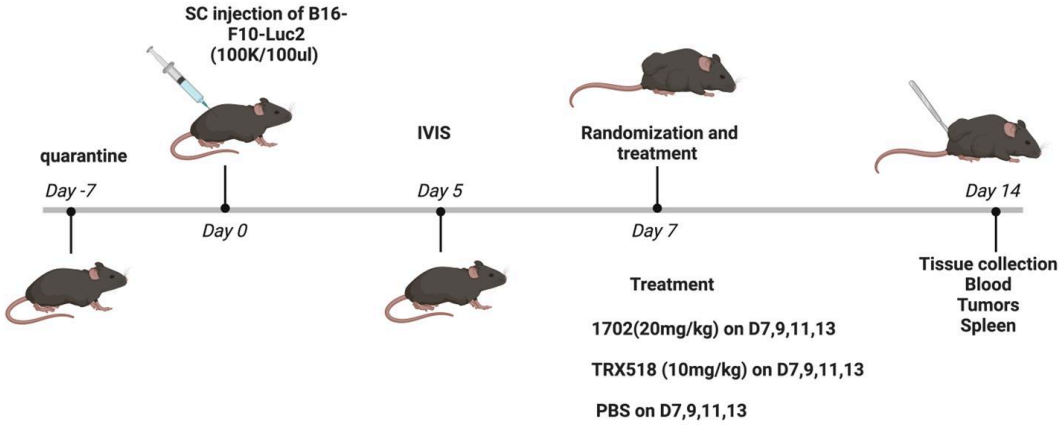
KROS-101 Treated T Cells Selectively Target GBM and CSCs



Source: Company materials

Role of KROS-101 in the immune profile of double humanized hGITR/hGITRL mice. For mouse model studies, double humanized GITR/GITRL mice bearing B16-F10-LUC2 tumors were treated with KROS-101 or controls. TILs were then analyzed by flow cytometry. Tumor size was measured by bioluminescence imaging and calipers. TILs isolated from treated mice were tested for cytotoxicity against B16-F10 cells.

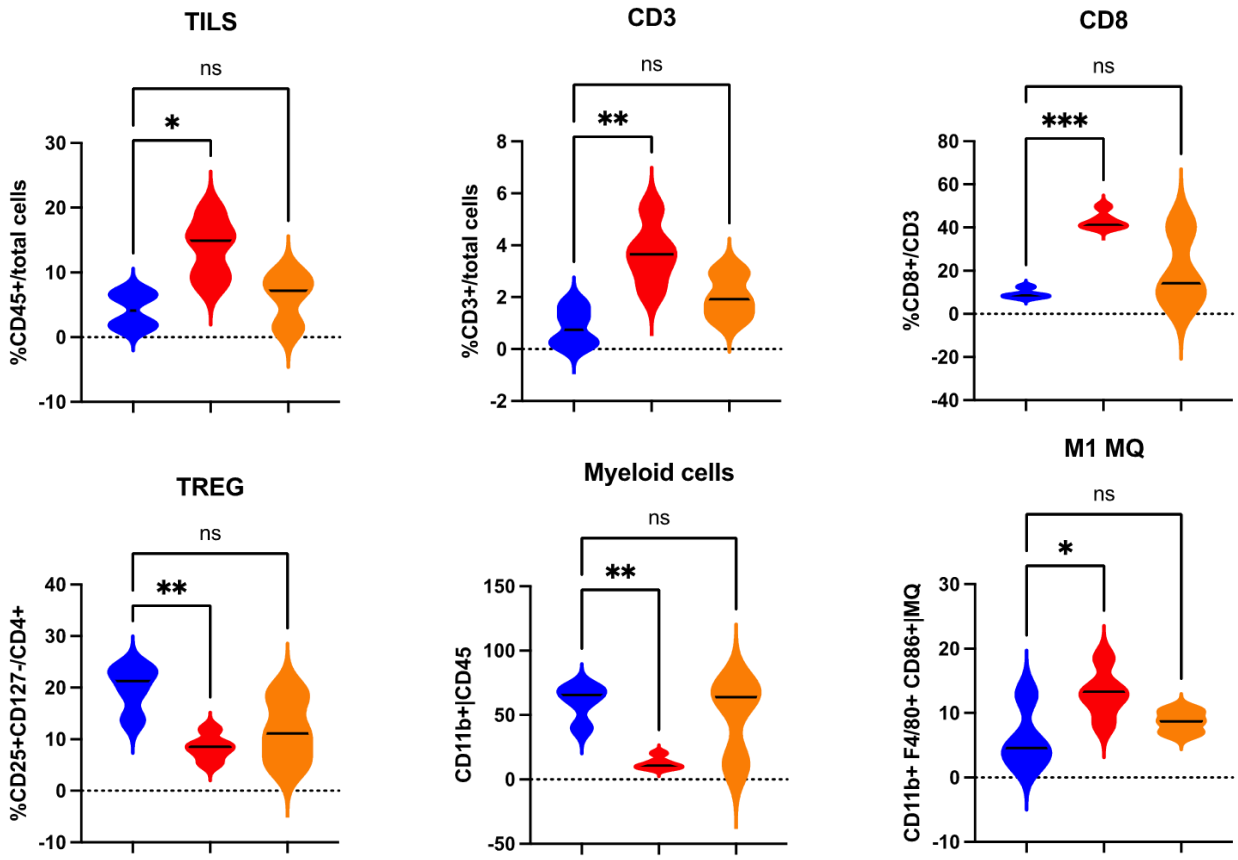
Timeline of B16-F10-LUC-2 Injection and Drug Treatment



Source: Company materials

The below flow cytometry analysis shows a reduction in regulatory T cells (Tregs, CD4+FoxP3+) and myeloid-derived suppressor cells (MDSCs) in KROS 101-treated tumors. Further, quantification of M1 macrophages (CD86+CD206−), shows enhanced polarization of macrophages toward the M1 phenotype in KROS-101-treated tumors.

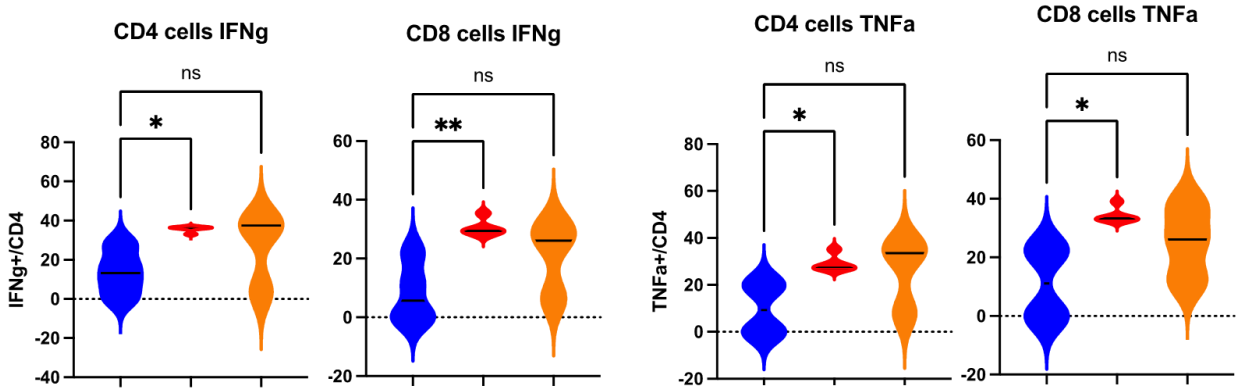
KROS-101 Enhances Tumor Immune Infiltration While Reducing Tregs and Myeloid Cells *in vivo*



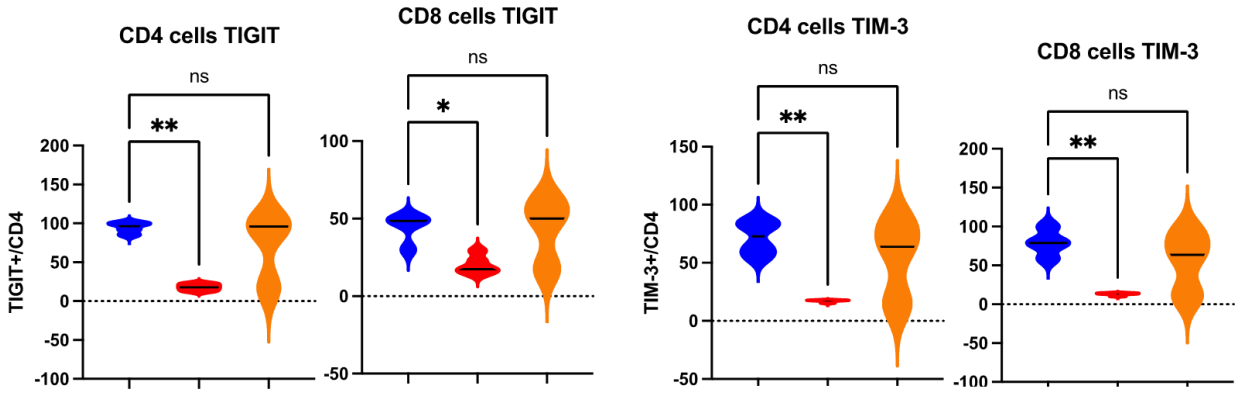
Source: Company materials

KROS-101 enhances cytotoxicity by increasing IFNγ and TNFα while reducing TIGIT and TIM3 *in vivo*. Quantification of IFN-γ and TNF-α production by CD4+ and CD8+ T cells isolated from melanoma tumors of KROS-101-treated mice, show significantly increased effector cytokine levels compared to PBS and TRX518 (Leap Therapeutics' GITR-specific agonistic mAb) treated controls. Flow cytometry analysis of immune checkpoint markers TIGIT and TIM-3 on CD4+ and CD8+ T cells, demonstrated a significant reduction in expression following KROS-101 treatment.

KROS-101 Increased Cytotoxic Markers (IFNγ and TNFα) in CD4+ and CD8+ T Cells *In Vivo*



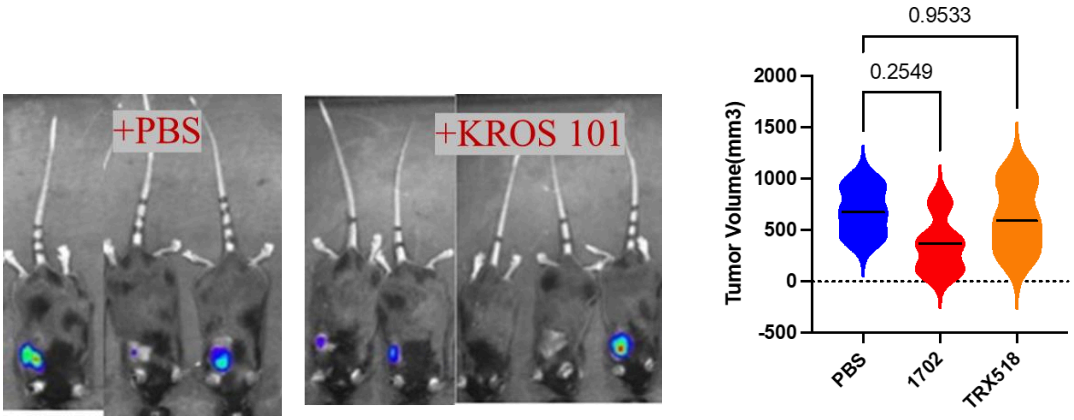
KROS-101 Decreased Exhaustion Markers (TIGIT and TIM3) in CD4+ and CD8+ T Cells *In Vivo*



Source: Company materials

KROS-101 treated mice saw reduced luminescence intensity of B16- F10-LUC2 (below right) compared to PBS treated mice. Quantification of tumor size after one week of treatment indicates that KROS-101 shows a stronger trend in tumor size reduction compared to TRX518.

KROS-101; Model Potential Effectiveness in Inhibiting Tumor Growth and Progression.



Source: Company materials

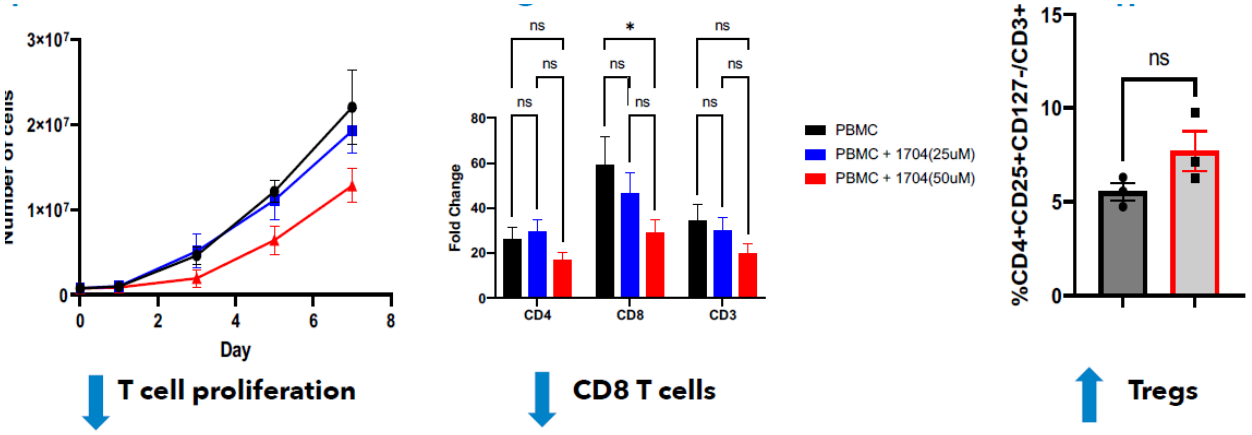
We believe further studies are warranted to evaluate the promise of KROS-101 in clinical studies, particularly as its dual action makes it a strong contender as a distinct cancer therapeutic from prior GITR targeting antibodies/agents. Unlike previous approaches that directly target GITR, Kairos is focusing on the GITR ligand which many engage distinct mechanisms leading to a more effective immune response. Further, the KROS-101 small molecule stabilizes the tertiary structure of GITRL (by stabilizing the trimer) ensuring full functional activation – unlike antibodies which are limited to a dimeric form and may not fully recapitulate native signaling. Most importantly, the totality of the preclinical data supports its distinction from comps, such as TRX518, by outperforming it in multiple assays and demonstrating:

- Increased CD8+ T cell activation
- Enhanced cytotoxicity against tumor cells
- Reduced T cell exhaustion
- Decreased Treg and myeloid suppressor cell populations

Taken together, these findings strengthen the validity of the Kairos approach and its potential to overcome the limitations observed in previous trials. KROS-101 is currently in pre-IND studies in development for a Phase 1 trial. The company is currently performing DMPK studies and expects to enter the clinic in early 2026. Whereas combination studies may make sense given the mechanism of action of the GITR ligand and concurrent co-stimulatory processes, the initial Phase 1 studies will be conducted as a monotherapy.

KROS-102: A novel GITR inhibitor set to tackle autoimmunity. Acting in an opposing fashion to KROS-101, KROS-102 is a GITR ligand antagonist designed to increase the inhibitory Treg functions while hampering T effector cell (killer T cells) numbers and function, which could reduce the overactive immune response observed in autoimmune diseases. Due to its central role in regulating Tregs, the GITR receptor complex is an optimal therapeutic target to treat autoimmunity. To this end, Kairos is developing a novel GITR inhibitor that can impact the abnormal immune responses against one's own body. By potently and specifically inhibiting an immune response, this strategy may impact autoimmune diseases. Currently, corticosteroids and chemotherapy are the main inhibitors of an immune response in many indications in the autoimmune space, but patients often must contend with harsh side effects including hip necrosis, gastritis and infections. Currently in preclinical studies, KROS-102 has been shown to decrease T effector cells and increase Treg cells in a dose dependent fashion.

KROS-102 Treatment Decreases T Cell Number and Activity



Source: Company materials

Regarding clinical plans for KROS-102, Kairos plans to target autoimmune diseases in which T cells play a critical role. This includes the possibility of systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Crohn's disease. As part of the IND-enabling studies the company will interrogate animal models of lupus and rheumatoid arthritis.

How do KROS-101 and KROS-102 fit into the broader landscape? By increasing T cell numbers and function KROS-101 may complement checkpoint inhibitors like pembrolizumab (Merck; MRK; not rated) and nivolumab (Bristol-Myers Squibb; BMY; not rated). By using the same mechanism of controlling T cell growth as KROS-101, but in the opposite direction, KROS-102 reduces T cell numbers and activity to potentially become a new class of agents for autoimmune diseases and transplant rejection. Given the market opportunity and large indications that KROS-102 could target, we envision a partnership with Big Pharma as a potential path forward. Although not part of our current valuation, both KROS-101 and KROS-102 represent significant potential upside for Kairos and its stock.

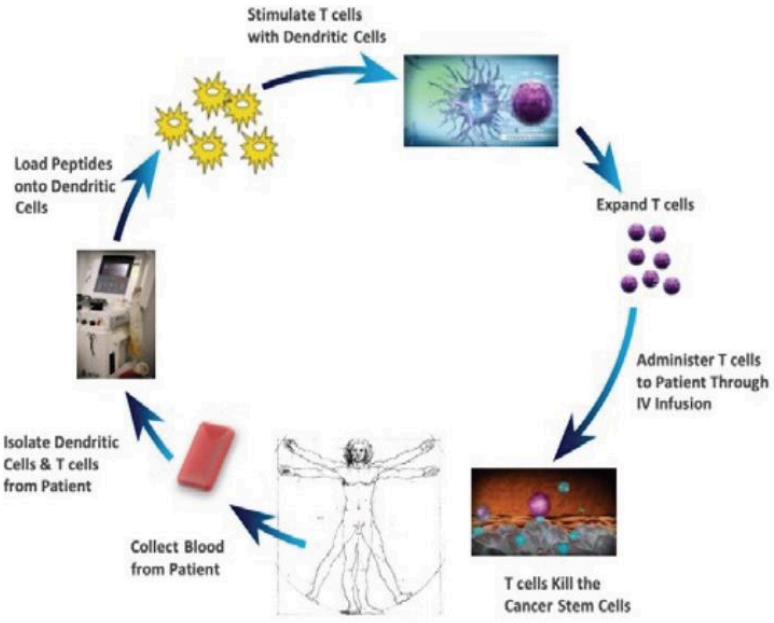
5. **Just getting started; Kairos has a deep preclinical oncology pipeline on deck to enter the clinic.**

Preclinical assets with near-term INDs round out the pipeline. In addition to its clinical, and near-clinical stage assets, Kairos is advancing three preclinical candidates, KROS-201, ENV- 205, KROS-301 and KROS-401, which we highlight in brief below. Of this pipeline, we expect KROS-201 to enter the clinic in 2025, as it recently cleared its IND to initiate a Phase 1 study of activated T cell therapy in GBM patients.

KROS-201: activating T cells via to tackle GBM. KROS-201 is a proprietary technology under development to produce activated T cells outside of the body for delivery to cancer stem cells (CSCs), for the treatment of glioblastoma (GBM), a highly malignant brain tumor that currently has limited therapeutic options with a median survival rate of 15-18 months and a five-year survival rate of less than 10%. KROS-201 seeks to become a novel T-cell therapy that allows a "plug and play" scenario wherein a patient's specific tumor can be addressed as well as the improvement of cancer treatment by stimulating patients' immune systems to generate a long-term population of cytotoxic T-cells and helper T-cells directed against the tumor. In the case of KRSO-201 treatment for GBM, as outlined in the diagram below, activated T cells (killer T cells) are first made from a patient's white blood cells in a cell culture system by activating with

cytokines or T-cell activating signals and by priming dendritic cells loaded with GBM CSC specific antigens. Activated T-cells can then be infused intravenously into patients with recurrent GBM.

KROS-201: A T Cell Therapy Activated by DCs to Treat GBM

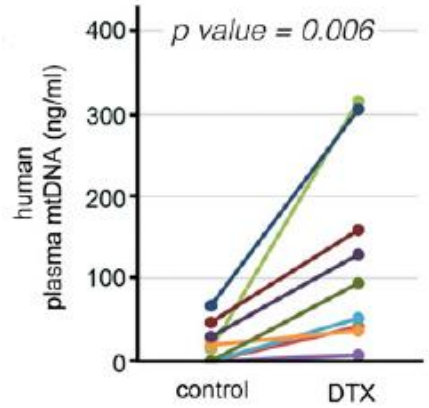


Source: Company materials

Kairos has completed IND-enabling pharmacology and toxicology studies and received IND clearance in 2022. The company has not yet initiated a trial for KROS-201, and management notes that it is currently prioritizing the clinical development of KROS-1-1, which will also be incorporated into the manufacturing of KROS-201.

ENV-205: mtDNA depletion to limit inflammation-induced pro-tumorigenic activity. Kairos is developing ENV-205 to reverse docetaxel chemotherapy resistance in prostate cancer via mitochondrial DNA (mTDNA) depletion. It is being designed as an antibody that can also limit the process of muscle wasting (cachexia) through the capture and excretion of mtDNA. Prostate cancer cells secrete greater concentration of mtDNA than noncancerous epithelial cells. Based on studies by Dr. Bhowmick and colleagues, prostate cancer cells secreted mtDNA to induce CAFs to generate anaphylatoxin C3a to support tumor progression in a positive feedback loop. Interestingly, the standard of care chemotherapy, docetaxel, used to treat CRPC was found to further potentiate this paracrine-signaling axis to mediate therapeutic resistance (figure below; DTX= docetaxel).

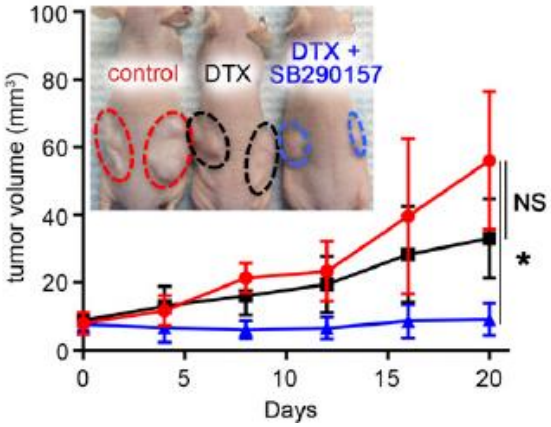
Docetaxel Induces Circulating mtDNA in Prostate Cancer



Source: Halder et al., PNAS 2020

Blocking anaphylatoxin C3a signaling, with an anaphylatoxin C3a receptor antagonist (SB290157), cooperatively sensitized prostate cancer tumors to docetaxel, and inhibited tumor growth in a mouse model of prostate cancer. Taken together, the data show that reciprocal paracrine signaling between prostate cancer cells and cancer associated fibroblasts promotes cancer progression and facilitates docetaxel resistance. Further, their initials findings suggest that docetaxel induced mtDNA secretion from cancer cells into the TME could be the paracrine-signaling molecule generated by prostate cancer cells to facilitate this process (Halder et al., *PNAS* 2020).

Synergistic Effect of Docetaxel and C3aR Antagonism Inhibit Tumor Expansion



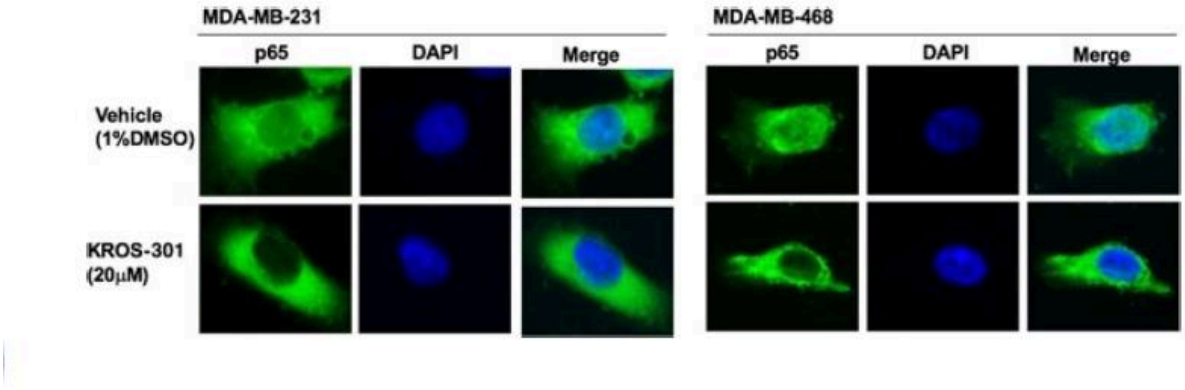
Source: Halder et al., PNAS 2020

While still in early preclinical development, ENV-205 is designed an antibody that targets the excretion of mtDNA found elevated in circulation when patients are on chemotherapy. Higher blood levels of mtDNA are not only associated with chemotherapy resistance but are more widely recognized as a mediator of cardiac toxicity and other systemic inflammatory events contributing to the negative side effects of chemotherapy use. Thus, depleting mitochondrial DNA with the administration of ENV-205 could potentially restore chemotherapy sensitivity and reduce its toxic side effects. Underscoring the potential of ENV-205, the company recently announced that through its academic partnership with Cedars-Sinai Medical Center,

it has received $600,000 in funding from the Department of Defense Lung Cancer Research Program to advance the development of ENV-205 treat chemotherapy drug resistance and cachexia, to ultimately counteract muscle loss, improve strength, and enhance the effectiveness of existing cancer treatments.

KROS-301 packs a one-two punch; targeting tumors with two distinct MoAs: KROS-301 is a tumor-targeting small molecule and checkpoint inhibitor with two distinct mechanisms of action resulting from blocking intranuclear localization of RelA, a key component of the NF-KB pathway (see immunofluorescence image b. NF-KB is a key component for cancer growth and drug resistance. KROS 301 targets tumor cells in in RelA/p65 biomarker positive solid tumors. The use of this biomarker enables choosing patients that will respond to the drug.

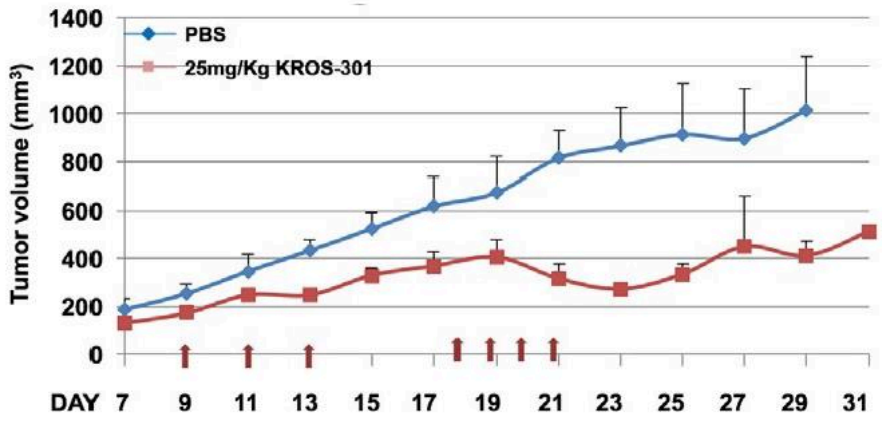
KROS-301 Blocks Intranuclear Localization of RelA/p65 in an *In Vitro* Breast Cancer Model



Source: Company materials

KROS-301 is in active preclinical development, and to start, Kairos is planning to evaluate KROS-301 for use in treating triple negative breast cancer. Early preclinical studies, highlighted below, demonstrate the tumor killing ability of KROS-301 in a mouse model of triple negative breast cancer.

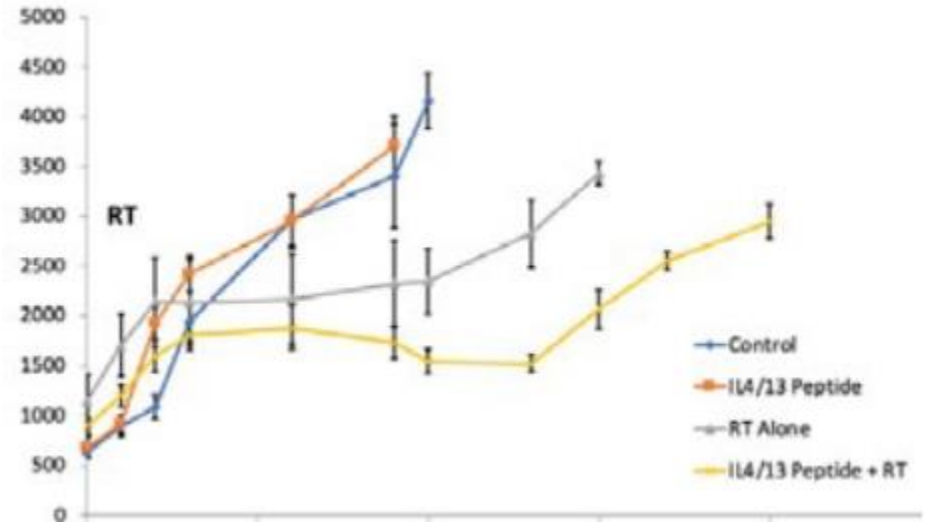
Efficacy of KROS-301 in a Triple Negative Breast Cancer Model in Inhibiting Tumor Growth



Source: Company materials

KROS-401: Converts pro-tumor macrophages into cancer-killing macrophages. KROS-401 is a TME immune modulator and cyclic peptide inhibitor of IL-4 and IL-13, reversing tumor associated macrophage inhibition. KROS-401 works to reduce the M2 macrophage population and limit fibrosis of the pancreas due to anti-inflammatory processes. Other indications may include pulmonary fibrosis, and other inflammatory conditions. Early preclinical work demonstrates that KROS-401 blocks the IL4/IL13 cytokine immune receptors for triple negative breast cancer and in addition, it increases anti-tumor response in conjunction with radiation therapy (RT) in an animal model (see figure below).

KROS-401 Aims to Enhance Anti-Tumor Response to Radiation Therapy in Breast Cancer



Source: Company materials

Macrophages in tumors are altered by the Th2 cytokines IL-4 and IL-13, inducing alternatively activated macrophages or M2. Breast cancer associated tumor associated macrophages are mainly activated M2 macrophages. Thus, shifting the balance toward M1 macrophages will prevent tumor growth and enable T-cell activation and killing, which is dependent on Th1 cytokines. The goal is to target a key Th2 cytokine pathway, IL-4, and IL-13 to block macrophage immunosuppression with KROS-401, thereby allowing T-cells to access tumors. There may be significant advantages to KROS-401 as the peptide binds to IL13R α1 and IL4R α1 (type I) receptor complex and blocks both IL-4 and IL-13 mediated signaling. The implication is that targeting IL-4Rα is predominantly for indications such as asthma or eczema, while the type I is for macrophages/tumor growth (esp IL13R). KROS-401 is currently in preclinical development.

Kairos Valuation

We are initiating coverage of Kairos with a Buy rating and $12 price target. We base our valuation on our probability-weighted clinical net present value (NPV) valuation model. This is an independent, fully taxed snapshot of each drug's perceived value in both the U.S. and E.U. We believe this method is appropriate in capturing the value of a company's assets, including early launches, by allowing us to flex multiple assumptions, including chance of success, peak sales estimates, and year of commercial launch.

Our peak sales estimates (market model below) are found by looking out approximately five to six years from projected drug launch. Per our market model below, and incorporating the vagaries, and timing of new drug launches, we believe a rough estimate of the market model sales in year five and year six best represent our view of peak. We believe a level of conservatism exists in our valuation model based on our assigned multiple of 17.0x, rather than the sometimes-inflated non-profitable biotech multiples in the 30-40x range. Our rationale for using Big Pharma multiples, plus a discount, is based on the potential acquisition metrics utilized by Big Pharma in valuing the smaller biotech as part of its overall portfolio. Our valuation is also based on fully diluted share count.

We consider two key factors when considering our valuation of Kairos using our NPV approach:

- We only value ENV-105 for mCRPC for the U.S. market, which has the potential to be a blockbuster indication for Kairos. We feel we are being conservative in our market model approach of ENV-105 by only attaining ~20% market penetration and ~$700 million peak sales, while still representing an unmet medical need.
- We purposefully omit the rest of Kairos' pipeline, including ENV-105 for NSCLC, which is already in the clinic. This represents a not only an additional layer of conservatism, but provides significant upside potential over the long-term by having multiple opportunities increasing the changes of potential success, in our belief.

Kairos NPV Valuation Model

	Indication	Status	Launch	POS	Peak Sales (US$M)	Economics	Profitability	NPV (US$)
ENV-105	mCRPC: U.S.	Phase 2	2030	20%	700	100%	30%	12.17
ENV-105	NSCLC	Phase 1						
KROS-101	Solid Tumors	Preclinical						
KROS-102	Auto-immune disease	Preclinical						
KROS-201	GBM	Preclinical						
KROS-301	TNBC	Preclinical						
KROS-401	TNBC	Preclinical						
ENV-205	Prostate Cancer	Preclinical						
							Total:	**12.17**

No current projections for Kairos' broad pipeline and multiple applicable indications. We believe this highlights significant conservatism of the overall pipeline's potential over the long-term, whiile reflecting the early stage nature of several of the assets

Source: H.C. Wainwright estimates.

Kairos ENV-105 U.S. mCRPC Market Model

ENV-105 U.S.: mCRPC	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
Total PC Incidence in U.S.	318,456	321,641	324,857	328,106	331,387	334,700	338,047	341,428	344,842	348,291	355,256
mCRPC	49,000	49,980	50,980	51,999	53,039	54,100	55,182	56,286	57,411	58,560	59,731
Penetration	3.0%	8.0%	12.0%	15.0%	18.0%	20.0%	25.0%	28.0%	30.0%	32.0%	35.0%
Number of patients treated	1,470	3,998	6,118	7,800	9,547	10,820	13,795	15,760	17,223	18,739	20,906
Cost of ENV-105 ($K)	$60.0	$61.8	$63.7	$65.6	$67.5	$69.6	$71.6	$73.8	$76.0	$78.3	$80.6
Revenue to Kairos ($M)	$ 83.8	$ 234.7	$ 369.9	$ 485.8	$ 612.5	$ 715.0	$ 938.9	$ 1,104.8	$ 1,243.6	$ 1,393.7	$ 1,601.4

Source: H.C. Wainwright estimates and SEER.

Risks

Clinical, regulatory, and market risk. The three primary risks for companies that are developing new therapeutic agents are: (1) regulatory risk including how the clinical data will be assessed by the FDA; (2) potential peers' competition; and (3) the risk of clinical trial failure. Additional regulatory challenges may be faced by the company, which could impede the potential success of a drug candidate. We value the competition and consider that potential comparable therapies may be developed from peers and could already be in later stages of development; however, we believe that Kairos' approach appears to be generating promising data as well as the potential to generate long term pipeline fill.

Financing risk. As with the majority of development stage biotechnology companies with no regulatory approved drug agents, maintaining funding is a critical necessity for the progression of the candidate pipeline. The company ended 3Q24 with $3.2 million in cash, from which we foresee significant dilution in the future as the company is in the early stages of its development with its broad pipeline. Cash burn could be significantly impacted based on increasing the number of development programs and potential offsetting by partner or collaborative milestone revenue payments. It is possible that additional equity raises could come in the future based on pipeline expansion and geography expansion.

Commercial risk. Even if approval is obtained for a therapeutic candidate, Kairos may not generate or sustain revenue from sales of the therapeutic product due to factors such as whether the therapeutic product can be sold at a competitive price and otherwise accepted in the market. Therefore, any revenue from sales of the therapeutic product may not offset the costs of development. The therapeutic candidates Kairos is developing are based on new technologies and therapeutic approaches. Market participants with significant influence over acceptance of new treatments, such as physicians and third-party payors, may not adopt a treatment based on its therapeutic products, and the company may not be able to convince the medical community and third-party payors to accept and use, or to provide favorable coverage or reimbursement for, any therapeutic products developed by Kairos and potentially existing or any future collaborators.

See company's SEC filings for additional disclosures.

($ in millions except per share data)

Profit & Loss	2022A	2023A	2024E	2025E	2026E	2027E	2028E
Licensing and R&D revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Milestone revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Product and Royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other revenues	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Revenues	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
CoGS	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Gross Profit	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Gross margin	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
G&A	0.5	1.6	1.8	1.7	2.1	4.0	6.3
R&D	0.1	0.1	0.1	5.2	8.1	18.1	34.5
Other op ex	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EBIT	**(0.6)**	**(1.7)**	**(1.9)**	**(6.9)**	**(10.1)**	**(22.1)**	**(40.8)**
EBIT margin	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*
Depreciation	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Amortization Intangibles	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EBITDA	**(0.6)**	**(1.7)**	**(1.9)**	**(6.9)**	**(10.1)**	**(22.1)**	**(40.8)**
EBITDA margin	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*
Non operating expenses	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Interest Income/Other	0.0	0.0	0.1	0.1	0.1	0.3	0.3
Interest expense	0.5	0.1	0.0	0.0	0.0	0.0	0.0
EBT	**(1.1)**	**(1.8)**	**(1.8)**	**(6.8)**	**(10.0)**	**(21.8)**	**(40.5)**
EBT margin	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*
Provision for taxes	0.0	0.0	0.0	0.0	0.0	0.0	(10.1)
Net Income	**(1.1)**	**(1.8)**	**(1.8)**	**(6.8)**	**(10.0)**	**(21.8)**	**(40.5)**
Participation of preferred stock	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Income to common	**(1.1)**	**(1.8)**	**(1.8)**	**(6.8)**	**(10.0)**	**(21.8)**	**(30.4)**
net margin	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*	*nm*
Number of shares - basic	10.2	10.4	13.6	16.2	25.4	39.2	45.0
Number of shares - diluted	10.2	10.4	13.6	16.2	25.4	39.2	45.0
EPS - basic	**(0.1)**	**(0.17)**	**(0.13)**	**(0.42)**	**(0.40)**	**(0.56)**	**(0.67)**
EPS - diluted	**(0.1)**	**(0.17)**	**(0.13)**	**(0.42)**	**(0.40)**	**(0.56)**	**(0.67)**

Source: SEC filings and H.C. Wainwright estimates.

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IPO September 16, 2024

Quarterly P&L

	Q3'24A	Q4'24E	FY'24E	Q1'25E	Q2'25E	H1'25E	Q3'25E	9M'25E	Q4'25A	FY'25E
Licensing and R&D revenue	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
Milestone revenue	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
Product and Royalties	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
Other revenues	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
Revenues	**0.00**	**0.00**	**0.0**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.0**
CoGS	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
Gross Profit	**0.00**	**0.00**	**0.0**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.0**
Gross margin	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
G&A	0.37	0.37	1.8	0.39	0.41	0.80	0.43	1.23	0.44	1.7
R&D	0.01	0.10	0.1	0.80	0.95	1.75	1.32	3.07	2.13	5.2
Other op ex	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
EBITDA	**(0.4)**	**(0.5)**	**(1.9)**	**(1.2)**	**(1.4)**	**(2.6)**	**(1.8)**	**(4.3)**	**(2.6)**	**(6.9)**
EBITDA margin			*nm*							*nm*
Non operating expenses	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
Net Interest Income/Other	(0.66)	(0.70)	0.1	0.03	0.03	0.05	0.03	0.08	0.03	0.1
Interest expense	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
EBT	**(1.0)**	**(1.2)**	**(1.8)**	**(1.2)**	**(1.3)**	**(2.5)**	**(1.7)**	**(4.2)**	**(2.5)**	**(6.8)**
EBT margin			*nm*							*nm*
Provision for taxes	0.00	0.00	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.0
Participation of preferred stock			0.0							0.0
Net Income to common	**(1.0)**	**(1.2)**	**(1.8)**	**(1.2)**	**(1.3)**	**(2.5)**	**(1.7)**	**(4.2)**	**(2.5)**	**(6.8)**
net margin			*nm*							*nm*
NoSH	10.91	13.83	13.59	13.87	13.90	13.89	18.20	15.32	18.74	16.18
NoSH	10.91	13.83	13.59	13.87	13.90	13.89	18.20	15.32	18.74	16.18
EPS - basic	**(0.10)**	**(0.08)**	**(0.13)**	**(0.08)**	**(0.10)**	**(0.18)**	**(0.09)**	**(0.28)**	**(0.14)**	**(0.42)**
EPS - diluted	**(0.10)**	**(0.08)**	**(0.13)**	**(0.08)**	**(0.10)**	**(0.18)**	**(0.09)**	**(0.28)**	**(0.14)**	**(0.42)**

Source: SEC filings and H.C. Wainwright estimates.

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Market Outperform (Buy): The common stock of the company is expected to outperform a passive index comprised of all the common stock of companies within the same sector.

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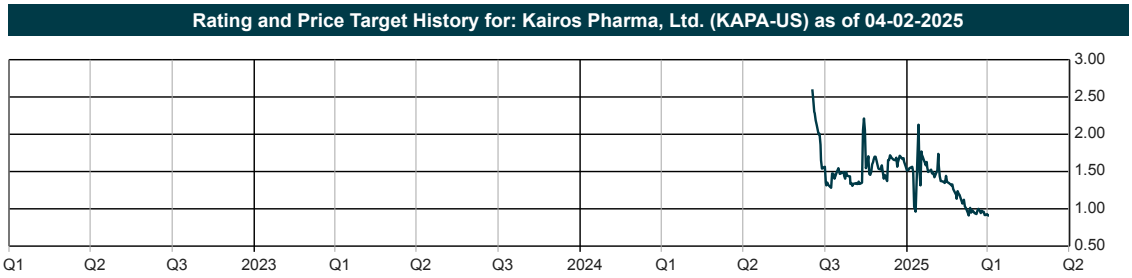

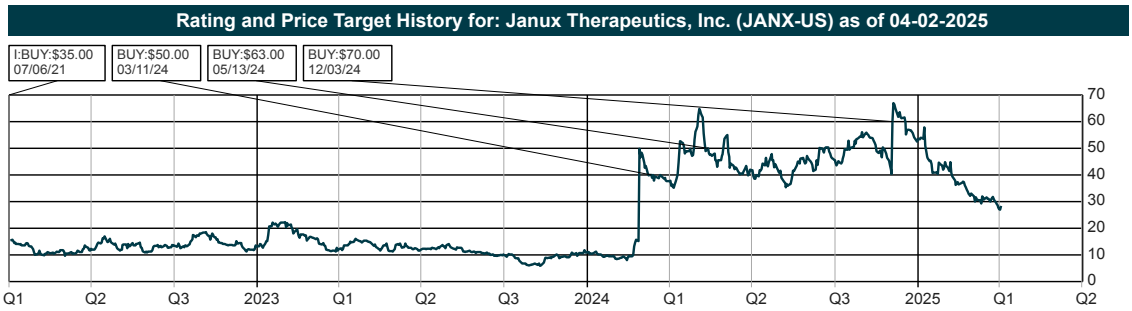

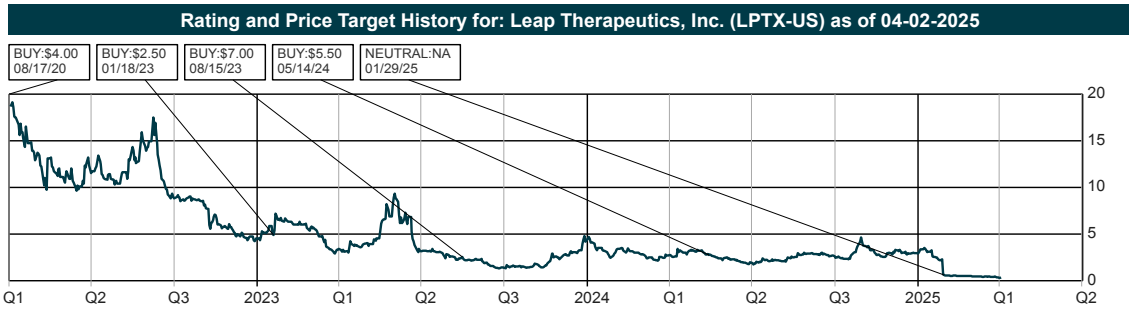

Related Companies Mentioned in this Report as of April/2/2025					
Company	Ticker	H.C. Wainwright Rating	12 Month Price Target	Price	Market Cap
Janux Therapeutics, Inc.	JANX	Buy	$70.00	$28.25	$1670
Leap Therapeutics, Inc.	LPTX	Neutral	$NA	$0.34	$14

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Distribution of Ratings Table as of April 2, 2025				
			IB Service/Past 12 Months	
Ratings	Count	Percent	Count	Percent
Buy	575	86.60%	130	22.61%
Neutral	84	12.65%	12	14.29%
Sell	0	0.00%	0	0.00%
Under Review	5	0.75%	2	40.00%

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