Rodman &Renshaw®

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Healthcare: Biotechnology

Kairos Pharma, Ltd. (KAPA)

INITIATING COVERAGE

KAPA: The Critical Moment to Target Cancer Drug Resistance

We are initiating coverage of Kairos Pharma, Ltd. (KAPA) with a Buy rating and a price target of $12. Kairos Pharma has created a new class of novel drugs that target drug resistance and checkpoints of immune suppression. The science underlying the intellectual property was developed at Cedars-Sinai Medical Center in Los Angeles. Kairos licensed patents from Cedars-Sinai Medical Center and Tracon Pharmaceuticals (TCON; Not Rated). The idea of focusing on "immune checkpoints" is currently quite trendy. After all, the human immune system can sense the difference between normal and foreign cells in the body and efficiently kills foreign cells while leaving normal cells undamaged. This is precisely why there exists "immune stop signs or checkpoints". However, cancer cells appear to be "clever" in finding ways to manipulate checkpoints to avoid being attacked by the immune system. The goal at Kairos is to unlock the immune system on two of the most pervasive problems in cancer treatment: resistance to therapy and immune suppression by cancer. Kairos possesses small molecules that specifically target immune checkpoints. Kairos also has an activated T cell therapy designed to transform a patient's T cells into activated killer T cells against cancerous stem cells. The biology of therapy resistance in cancer is fascinating. This is especially true in prostate cancer. We would encourage you to consider reading into metastases and mechanisms of resistance below.

The anti-endoglin antibody known as ENV105 (carotuximab) is Kairos' lead asset in clinical trials. Endoglin (CD105) is a member of the transforming growth factor-beta (TGF-beta) receptor family that binds strongly to TGF-beta1 and -beta3 but significantly less strongly to TGF-beta2. Endoglin has a crucial role in angiogenesis and, therefore, is an important protein for tumor growth, survival, and metastasis. Expression of CD105 is low in resting endothelial cells. But this changes once neoangiogenesis initiates and endothelial cells become active in places like tumor vessels. CD105 (endoglin) is expressed by both cancer cells and cancer-associated fibroblasts. Kairos is utilizing ENV105 first in prostate cancer. ENV105 binds to CD105. In front-line prostate cancer treatment is the use of agents to block androgen signaling. We discuss this in detail below. However, almost all patients become resistant to androgen signaling inhibition. Interestingly, CD105, as a receptor, is elevated upon androgen receptor signaling inhibition (e.g., enzalutamide treatment). While both cancer-associated fibroblasts (CAF) and cancer cells are quite heterogeneous, a large proportion of them express CD105 in response to androgen receptor (AR) inhibition. Anti-Endoglin is designed to address resistance in chemotherapy, radiation therapy, androgen-targeted therapy, EGFR inhibitors, and checkpoint inhibitors when given in combination with other agents. For example, blocking CD105 with carotuximab (ENV105) reverses resistance to enzalutamide, abiraterone, and apalutamide as androgen signaling inhibitor therapies in prostate cancer (Figure 1 on Page 3). Androgen signaling is by far the dominant mechanism of prostate cancer growth. Using an agent such as ENV105 that targets tumor-associated fibroblasts as well as cancer cells to limit resistant mechanisms and can reasonably extend androgen signaling inhibition sensitivity.

Kairos believes ENV105 to be suited for those patients failing first-line AR inhibition, which happens about 18 months from the start of hormone therapy. A phase II trial in roughly 90 patients is ongoing and a read-out is anticipated in Q125. By giving ENV105 with second-

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Stock Data

Rating	Buy
Price Target	$12.00
Exchange	NYSE American
Price	$1.66
52-Week High	$4.00
52-Week Low	$1.22
Cash (M)	$3
Market Cap (M)	$21
Shares Outstanding (M)	13
3 Month Avg Volume	329,164

Estimates

	2024E	2025E
	(Curr.)	(Curr.)
Revenue (M) | $ | Year end: December		
Q1	0.0A	0.0E
Q2	0.0A	0.0E
Q3	0.0A	0.0E
Q4	0.0E	0.0E
FY	0.0E	0.0E
EPS | $ | Year end: December		
Q1	-	(0.14)E
Q2	-	(0.27)E
Q3	(0.08)A	(0.36)E
Q4	(0.10)E	(0.36)E
FY	(0.18)E	(1.15)E

One Year Performance Chart

line hormone therapy, one could potentially extend the current median 2 months of efficacy to something significantly longer; early data suggests this is possible.

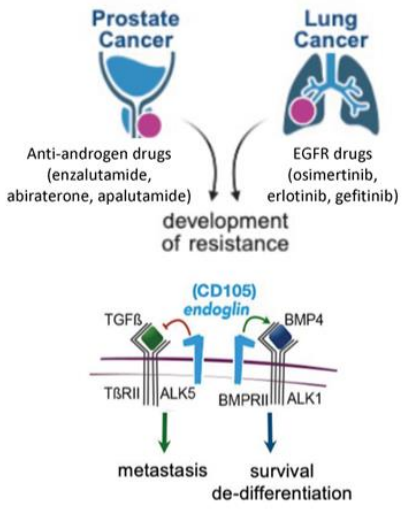
Further, there is evidence that carotuximab also can reverse anti-EGFR therapies like osimertinib. Approximately 15-20% of non-small cell lung cancer (NSCLC) patients develop mutations in the epidermal growth factor receptor (EGFR) that can be targeted by tyrosine kinase inhibitors such as osimertinib (AstraZeneca; AZN; Not Rated). However, much like prostate cancer, patients treated with osimertinib eventually become resistant. The goal of adding ENV105 is to make osimertinib-resistant patients once again sensitive to treatment. A phase I study in osimertinib-resistant EGFR mutated NSCLC is enrolling up to 60 patients. Initial data may be available in 2H 2025.

Kairos had $3.2M in cash as of September 30, 2024. The company will need to raise additional capital to be able to conduct registration-enabling trials in one or more indications.

Our Buy rating and $12 price target are driven by a risk-adjusted net present value analysis of the utility of ENV105 in: (1) metastatic castration-resistant prostate cancer patients who are failing first-line androgen receptor inhibition therapy (late-2028/early-2029 launch; ~$5.5B peak sales in 2034-35; 50% POS; contributes ~$9 to our PT;) and (2) EGFR-mutated NSCLC after frontline osimertinib failure (late-2029/early-2030 launch; ~$1.1B peak sales in 2035-36; 45% POS; contributes ~$2 to our PT). We also account for a modest risk-adjusted royalty contribution from a potential commercialization partner in ex-US regions (contributes ~$1 to our PT). Given Kairos' current cash position and requirement to raise additional cash to be able to conduct registration trials in one or more indications, we apply an 18% discount rate. Our assumptions are subject to change if warranted by the availability of new information. Potential impediments to our rating and price target are outlined in the risks section of this report.

Kairos Pharma: A Synopsis and Portfolio

Figure 1. A Possible Means to Overcoming Cancer Drug Resistance



Source: Kairos Pharma Corporate Deck

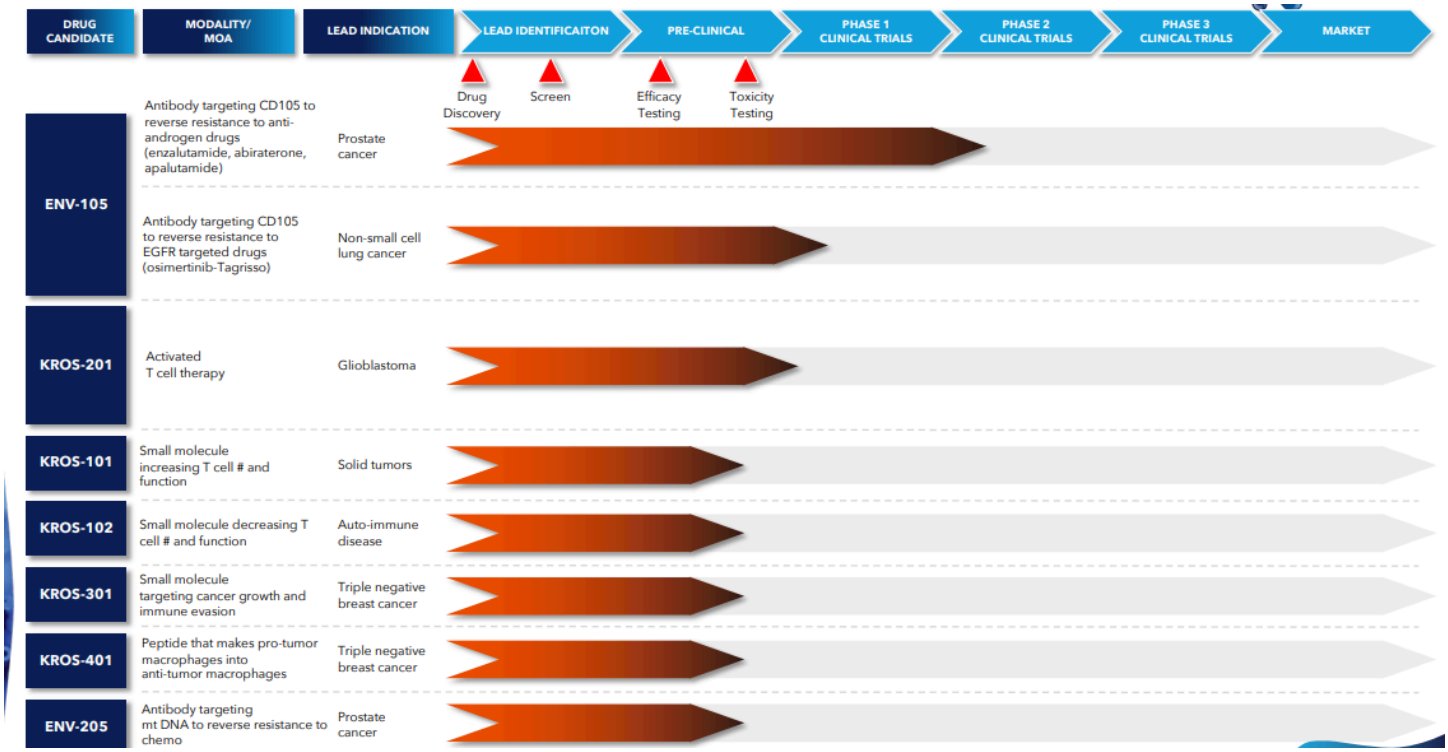
In September 2023 Kairos began enrolling patients in a phase 1 trial for EGFR-mutated non-small cell lung cancer who had become resistant to osmertinib and/or in patients who are incompletely treated with osmertinib and maintain tumor ctDNA. The readout will be for safety and a recommended phase 2 dose as well as biomarkers that could enrich for an ideal patient population.

In May 2024, the Chief Scientific Officer of Kairos, Neil Bhowmick, Ph.D.,who is also a Professor at Cedars-Sinai Professor of Medicine, was awarded a $3.2M grant from the National Institutes of Health (NIH) to support the development of the mechanism of action and companion biomarkers. This work is being performed by Cedars-Sinai in conjunction with the ongoing phase 2 trial for ENV105 and apalutamide in castrate resistant prostate cancer patients. The funding is being used to enrich for biomarker positive patients who will potentially respond to ENV105.

Kairos has a number of additional compounds in preclinical development (Figure 2). Kairos has collected several compounds whose mechanism is believed to overcome current therapeutic failures resulting from resistant or refractory disease. Figure 3 provides a rationale for each Kairos compound. The mechanism of action for each compound in the portfolio is depicted in Figure 4.

Kairos has used ENV105 to address the impact of the activation of the hypoxia response (HIF1a) as it is initiated with hormone therapy for prostate cancer, chemotherapy for ovarian cancer, irradiation for head and neck cancer, and EGFR-inhibition in lung cancer. It has long been known that HIF1a activation is associated with therapy resistance; it is likely this activation of CD105 expression that is the reason for this observation. As CD105 is the target for ENV105 in both tumor cells and tumor associated fibroblasts, Kairos have chosen to combine ENV105 with existing therapy to slow down or abrogate disease progression and overcome treatment resistance.

Figure 2. Kairos Product Portfolio



Source: Kairos S-1 2024

Figure 3. Kairos Provides a Rationale for Six Molecules Within its Portfolio

UNMET MEDICAL NEED	DRUG	HOW KAIROS ADDRESSES UNMET MEDICAL NEED
Development of resistance to many, otherwise effective, cancer drugs (hormone based therapies, EGFR-based therapies, radiation, and other specific chemotherapies)	ENV105	• ENV105 inhibits CD105 (CD105 is the protein responsible for cancer drug resistance in various forms of cancer) • Currently in Phase 2 trial in prostate cancer and Phase 1 trial in lung cancer
T cells drastically reduced by cancer	KROS101	• KROS101 uses a novel dual mechanism to increase killer T effector cells and reduce suppressor T reg cells (T cells have 2 types cells: those that kill cancer cells and those that inhibit the killer T cell response)
In autoimmune diseases, T cells are overactive against normal cells	KROS102	• KROS102 has the opposite effect of KROS101, by decreasing the number of overactive T effector cells and increasing suppressor T reg cells
Immunosuppression from cancer	KROS201	• KROS201 are killer T cells generated outside of the immunosuppressed body which then is delivered directly to the cancer stem cells that drive cancer growth. • Currently cleared for IND (investigational new drug application) by FDA
Chemotherapies are untargeted and immunosuppressive	KROS301	• By targeting the NF-kB molecular pathway, KROS 301 kills tumors and inhibits the mechanism of PD-L1 expression on tumor cells (PD-L1 is a "checkpoint inhibitor" that prevents T cells from killing the cancer)
Tumor environment is immunosuppressive from macrophages (a type of white cell that can be either anti-cancer or pro-cancer)	KROS401	• KROS401 targets pro-cancer macrophages to convert them into anti-cancer macrophages

Source: Kairos Investor Presentation, 2024

Figure 4. Kairos Portfolio Molecules Mechanism of Action

DRUG	MECHANISM OF ACTION
ENV 105	• Antibody that targets CD105 (Endoglin) by inhibiting BMP signaling to reverse cancer drug resistance • Papers: Kato et al., Madhav et al. (Science behind ENV105), Smith et al (Phase II trial results) • Other papers not by our group: Schoonderwoerd et al. shows the synergy with checkpoint inhibition of CD105 targeting and Wu et al. discusses synergy of ENV105 with immunotherapy.
KROS 101	• Small molecule agonist for GITR ligand • Papers: Zhou et al. (Human) hGITR PNAS paper of Ram Murali showing crystal structure of the human GITR ligand used to develop KROS 101 agonist and KROS 102 antagonist. Zhou et al. (Mouse), PNAS paper showing mouse GITR activation by Ram's group (our VP of Research and Development) through structural biology.
KROS 102	• Small molecule antagonist for GITR ligand • Papers for KROS101 is relevant but this antagonist prevents GITR ligand from working inhibiting T cell growth
KROS 201	• Activated T cells targeting glioblastoma cancer stem cell antigens • Papers: Miyaguchi et al. shows translational development of activated T cell technology, Wen et al., Clin Cancer Research paper is the randomized multi-institutional phase II study showing that a multi-epitope DC vaccine significantly improves progression free survival. We use 6 of the antigens in our activated T cell technology, and also add 3 more CTL antigens and 9 helper epitopes in order to improve the robustness of the immunogenicity, Yuan et al. Oncogene paper is our first report of isolation of cancer stem cells from glioblastoma which is the target cell in KROS 201, Xu et al. Stem Cell paper shows strategy of immunologically targeting cancer stem cells and demonstrates some of the antigens overexpressed on glioblastoma cancer stem cells.
KROS 301	• Small molecule inhibiting relA nuclear translocation in the NF-kB molecular pathway in dependent cancers • Paper: Kanzaki et al., BCTT paper showing KROS 301 in triple negative breast cancer model
KROS 401	• Cyclic peptide inhibits IL-4 and and IL-13 receptors on macrophages to reverse M1 to M2 transition • Paper: Xue et al. IL4- IL13 inhibitor paper in Nature Communications showing KROS 401 activity in a chronic pancreatitis model reversing M1 to M2 transition in macrophages
ENV 205	• Mitochondrial DNA depletion to reverse doxetaxel chemotherapy resistance • Paper: Halder et al., PNAS paper showing mechanism of action of ENV 205

Source: Kairos Investor Presentation, 2024

ENV105, as we have mentioned above**,** demonstrated an ability to target CD105 which is elevated in drug resistance in prostate cancer. Androgen therapy resistance in prostate cancer is being targeted in the Phase 2 trial. The ENV105 Phase 2 trial in prostate cancer with apalutamide (Janssen; JNJ; Not Rated) is a multicenter trial being conducted at Cedars-Sinai, University of Utah, and City of Hope. EGFR antagonist resistance in lung cancer is also being targeted in a Phase 1 trial in combination with osimertinib is being conducted at Cedars-Sinai.

KROS 101 is a small molecule orally available GITR (glucocorticoid-induced tumor necrosis factor receptor) ligand antagonist designed to deplete suppressive regulatory T-cells (T_{regs}) and activate effector T-cells to augment the antitumor immune response. KROS 101 is being developed as a systemic immune modulator to address immunosuppressive activity of solid cancers.

GITR is a powerful checkpoint that suppresses the immune response against cancer. KROS 101 stabilizes the GITR ligand to signal GITR to impact cancer therapy. GITR is a checkpoint, a central switch that promotes "killer" effector T-cell functions and hampers inhibitory T_{reg} functions. Due to its central role in regulating T_{regs}, the GITR receptor complex is considered an optimal therapeutic target for treating cancer. This may be the optimal complement to add to current checkpoint inhibitors as it shows a dose dependent effective response in increasing the immune response. As a competitive antagonist, KROS 101 could be dosed to avoid the typical common side effects of checkpoint inhibitors. There is the belief that the 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 T_{reg} cells, the suppressive activity of T_{reg} 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, our 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. The analogy is a digital signal rather than a limited analog signal. This powerful

physiologic signal can lead to exponential signaling of T-cells to proliferate against cancer cells. In addition, the small molecule half-life enables reversibility, and can be modulated to limit side effects. Having both agonist and antagonist molecules can reverse potential untoward effects. Further it is oral. The discovery of KROS 101 was the culmination of transformative structural biology based on crystallography first used to model GITR ligand by Kairos' scientists. KROS 101 is currently in pre-IND studies in development for a Phase 1 trial.

KROS 102 is a GITR antagonist designed to increase the inhibitory T_{reg} functions, while hampering T effector cell numbers and function. KROS 102 has been shown to decrease T effector cells and increase T_{reg} cells in a dose dependent fashion to treat autoimmune diseases. This novel GITR inhibitor is thought to impact the abnormal immune responses against one's own body. Due to its central role in regulating T_{reg}, the GITR receptor complex is an optimal therapeutic target to treat autoimmunity. By potently and specifically inhibiting an immune response, this strategy may impact autoimmune diseases such as Crohn's disease, multiple sclerosis, and rheumatoid arthritis. KROS 102 has been shown to decrease T effector cells and increase T_{reg} cells in a dose dependent fashion. KROS 102 is currently in preclinical studies.

KROS 201 is a proprietary technology for the production of activated T-cells. Activated T-cells are killer T-cells that are made from a patient's white blood cells in a cell culture by activating with cytokines or T-cell activating signals and by priming dendritic cells loaded with glioblastoma cancer stem cell specific antigens. Kairos generates activated T-cells that can be infused intravenously into patients with recurrent glioblastoma. KROS 201 begins with the activation of T-cells using dendritic cells for the treatment of patients with glioblastoma. Cytotoxic and helper T-cells are generated in a cell manufacturing center and infused into patients with recurrent glioblastoma. Kairos believes KROS 201 has the potential to become a novel T-cell therapy that allows a "plug and play" scenario where 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. Kairos has completed IND-enabling pharmacology and toxicology studies and submitted an IND application.

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. 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 401 is a tumor microenvironment immune modulator and cyclic peptide inhibitor of IL-4 and IL-13 reversing tumor associated macrophage inhibition. KROS 401 reduced the M2 macrophage population and limits fibrosis of the pancreas due to anti-inflammatory process.[1] Other indications may include pulmonary fibrosis, and other inflammatory conditions. 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 in an animal model. Recently, it became clear that 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 in preclinical development.

[1] Xue J, Sharma V, Hsieh MH, *et al.* Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. *Nat Commun*. 2015;6:7158. Published 2015 May 18. doi:10.1038/ncomms8158

Biology of Endoglin and ENV105

Endoglin and Antibodies to Endoglin-the Early Days

A paper in 1986 by Yuro Haruta and Ben Seon from the Roswell Park Institute in Buffalo reported on the generation and characterization of a monoclonal antibody termed SN6 that was found to define a distinct human leukemia-associated cell surface glycoprotein. SN6 reacted with non-T-cell acute lymphoblastic leukemia cells and myelomonocytic leukemia cells but did not react with various normal cells from healthy donors. Haruta and Seon characterized SN6 for its target cell in human leukemogenesis.[2] The cell surface glycoprotein identified by SN6 became known as GP160. The authors hypothesized that GP160 was either a marker of pluripotent stem cells or a marker of stem cells common to lymphoid and myeloid cells.

In a paper by Seon and others, researchers had subsequently proven that the antibody SN6 bound not to GP160 but to CD105 or endoglin.[3] SN6 was found to react with immature human B-lineage leukemia cells (mainly acute lymphoblastic leukemia cells) and myelomonocytic leukemia cells but did not react with other types of leukemia/lymphoma cells.[2] Expression of endoglin is highly consistent between fresh leukemia cells from patients and cultured leukemia cell lines of the same phenotypes. Such consistent expression of endoglin was not observed for carcinoma cells. SN6 did not show significant reaction with normal peripheral blood cells tested, which included B-cells, T-cells, granulocytes, monocytes and erythrocytes. However, it reacted with roughly 1% of the population of normal bone marrow cells.[2]

Seon and colleagues tested approximately 100 malignant tissues from a variety of cancers by immunohistochemical (IHC) staining using SN6 and other anti-endoglin antibodies that bound to other epitopes. IHC results suggested solid tumor cancers including breast, colorectal, lung, prostate, brain, bladder, ovary and thyroid revealed reactivity of anti-endoglin antibodies was restricted to vascular endothelium but these antibodies did not react with tumor cells “per se” in the tissues.[3]

Anti-endoglin antibodies (SN6 derivatives) conjugated with ricin were able to stop tumor growth in a breast cancer (MCF-7) SCID (severe combined immunodeficiency) animal. The mechanism by which anti-endoglin antibodies suppress tumor growth was determined to be through suppression of blood vessel or angiogenesis in the mice. Antibodies were more effective for tumor suppression in immunocompetent mice rather than SCID mice suggesting that T-cell immunity is important for effective antitumor efficacy *in vivo*.[3]

The authors concluded that the tissue distribution pattern and functional properties of endoglin support it to be a promising target in anti-angiogenesis therapy of solid tumors. This hypothesis was also supported by studies of selected anti-endoglin antibodies and their immunoconjugates in tumor-bearing mice. For studies in humans, the authors created a human/mouse chimeric antibody they called c-SN6j. Pharmacokinetic studies and studies in nonhuman primates have occurred. The results suggest c-SN6j can be safely administered to patients with tumors. c-SN6j was renamed TRC105 by Tracon Pharma.[3]

[2] Haruta Y, Seon BK. Distinct human leukemia-associated cell surface glycoprotein GP160 defined by monoclonal antibody SN6. *Proc Natl Acad Sci U S A*. 1986;83(20):7898-7902. doi:10.1073/pnas.83.20.7898

[3] Seon BK, Haba A, Matsuno F, *et al.* Endoglin-targeted cancer therapy. *Curr Drug Deliv*. 2011;8(1):135-143. doi:10.2174/156720111793663570

ENV105 and Prostate Cancer

Tumor Progression, Metastasis and Carcinoma-Associated Fibroblasts in Prostate Cancer

The rise in prostate-specific antigen (PSA) is considered the marker indicating disease recurrence in prostate cancer following prostatectomy or radiation ablation of the prostate. The standard of care for recurrent prostate cancer is the interruption of androgen signaling. Yet like many cancers, resistance to androgen signaling deprivation therapy (ADT) has no cures. It is believed that early in the initiation of prostate cancer, stromal tissue surrounding the site of tumor initiation begin to "co-evolve" with cancer progression. There are tumor-inductive properties that appear able to convert non-tumorigenic epithelial to tumors in a process known as the "epithelial-mesenchymal transition". These cancer-associated fibroblasts (CAF) promote tumor growth and progression.[4,5,6] Neil Bhowmick and colleagues at Cedars Sinai, through a series of xenografts, demonstrated that a heterogenous mixture of mouse stromal fibroblasts coupled with intact though deficient TGF-β (transforming growth factor beta) signaling were able to induce transformation of benign epithelia into malignant lesions.[7] Histologically heterogenous fibroblastic cells vary and surface proteins can be used to differentiate among distinct fibroblastic cell populations. Among the different surface proteins within mesenchymal stem cell proteins is endoglin (CD105). CD105 is a TGF-β type III receptor that functions in promoting bone morphogenic protein (BMP) signaling and antagonized TGF-β signaling.[8] Kato and colleagues hypothesized that the CD105+ cancer-associated fibroblast population critically mediates prostatic tumor epithelial differentiation and castrate resistance.[9]

Cellular Heterogeneity in Carcinoma-Associated Fibroblasts Determine its Tumor Supportive Property

Kato *et al.* sought to determine if the stromal fibroblastic CD105 population in tissues and primary cells was significantly associated with epithelial neuroendocrine differentiation. This hypothesis was confirmed from prostatectomy tissues with cultured cancer-associated fibroblasts (CAFs) and normal-associated fibroblasts (NAFs). Primary CAF cultures from prostatectomy tissues can promote the expansion of established tumor epithelia. Routine culturing of primary prostate CAF can lead to its loss of tumor-promoting potential.[9]

Kato compared primary cultured NAF, low passage CAF and high passaged (>8 passages) CAF^{HIP} using FACS to determine the composition of CD90, CD105, CD117 and Stro-1 among the fibroblast populations. For reference note that Stro-1 is a surface protein marker of mesenchymal stem cells. CD117 or c-Kit is expressed on bone-marrow derived stem cells but also on organs as prostate, liver and heart. CD90 is a 25-37 kDa protein which plays a dominant role in the fibrotic and pro-inflammatory state. CD90 fibroblasts influence the disease process of malignant tumors.[10] Figure 5 provides data on differences in the composition between the three types of fibroblasts. The most abundant fibroblast population within the NAF and CAF groups were CD90 and CD105. Compared to the CAF^{Hip} group (Figure 5A). In Figure 5B the prevailing notion that prostatic fibroblasts can induce epithelial cell expansion, xenografts of human prostate cancer epithelia alone resulted in no tumor growth compared to tissue recombinant grafts with stromal fibroblastic cells.

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[4] Hayward SW, Wang Y, Cao M, *et al.* Malignant transformation in a nontumorigenic human prostatic epithelial cell line. *Cancer Res*. 2001;61(22):8135-8142.

[5] Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR. Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. *Cancer Res*. 1999;59(19):5002-5011. doi:10.1186/bcr138

[6] Gleave M, Hsieh JT, Gao CA, von Eschenbach AC, Chung LW. Acceleration of human prostate cancer growth *in vivo* by factors produced by prostate and bone fibroblasts. *Cancer Res*. 1991;51(14):3753-3761.

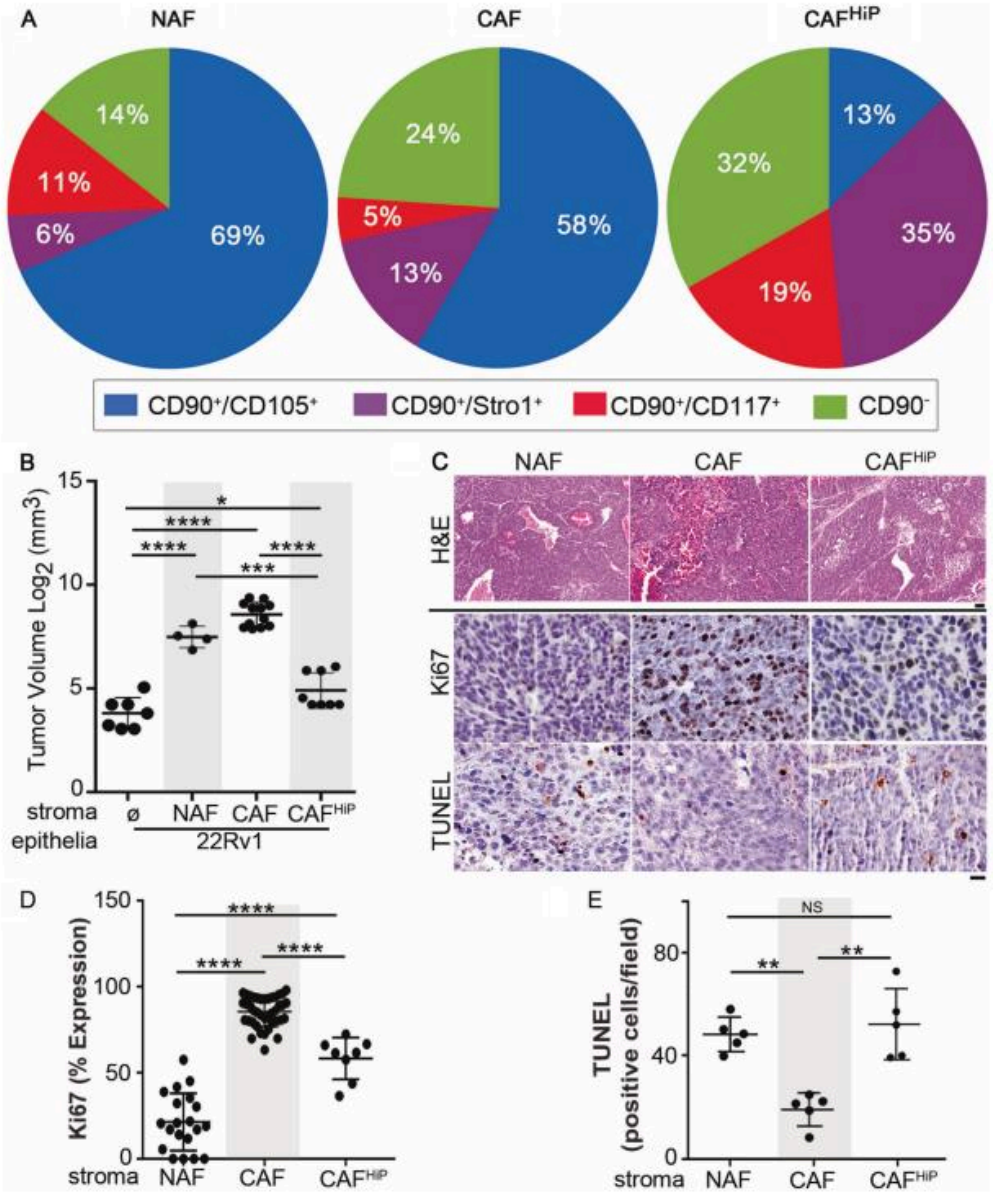
[7] Kiskowski MA, Jackson RS 2nd, Banerjee J, *et al.* Role for stromal heterogeneity in prostate tumorigenesis. *Cancer Res*. 2011;71(10):3459-3470. doi:10.1158/0008-5472.CAN-10-2999

[8] Fonsatti E, Altomonte M, Nicotra MR, Natali PG, Maio M. Endoglin (CD105): a powerful therapeutic target on tumor-associated angiogenetic blood vessels. *Oncogene*. 2003;22(42):6557-6563. doi:10.1038/sj.onc.1206813

[9] Kato M, Placencio-Hickok VR, Madhav A, *et al.* Heterogeneous cancer-associated fibroblast population potentiates neuroendocrine differentiation and castrate resistance in a CD105-dependent manner. *Oncogene*. 2019;38(5):716-730.

[10] Zeng F, Gao M, Liao S, Zhou Z, Luo G, Zhou Y. Role and mechanism of $CD90^{+}$ fibroblasts in inflammatory diseases and malignant tumors. *Mol Med*. 2023;29(1):20. Published 2023 Feb 6. doi:10.1186/s10020-023-00616-7

Figure 5. Stromal Heterogeneity in Tumor Progression

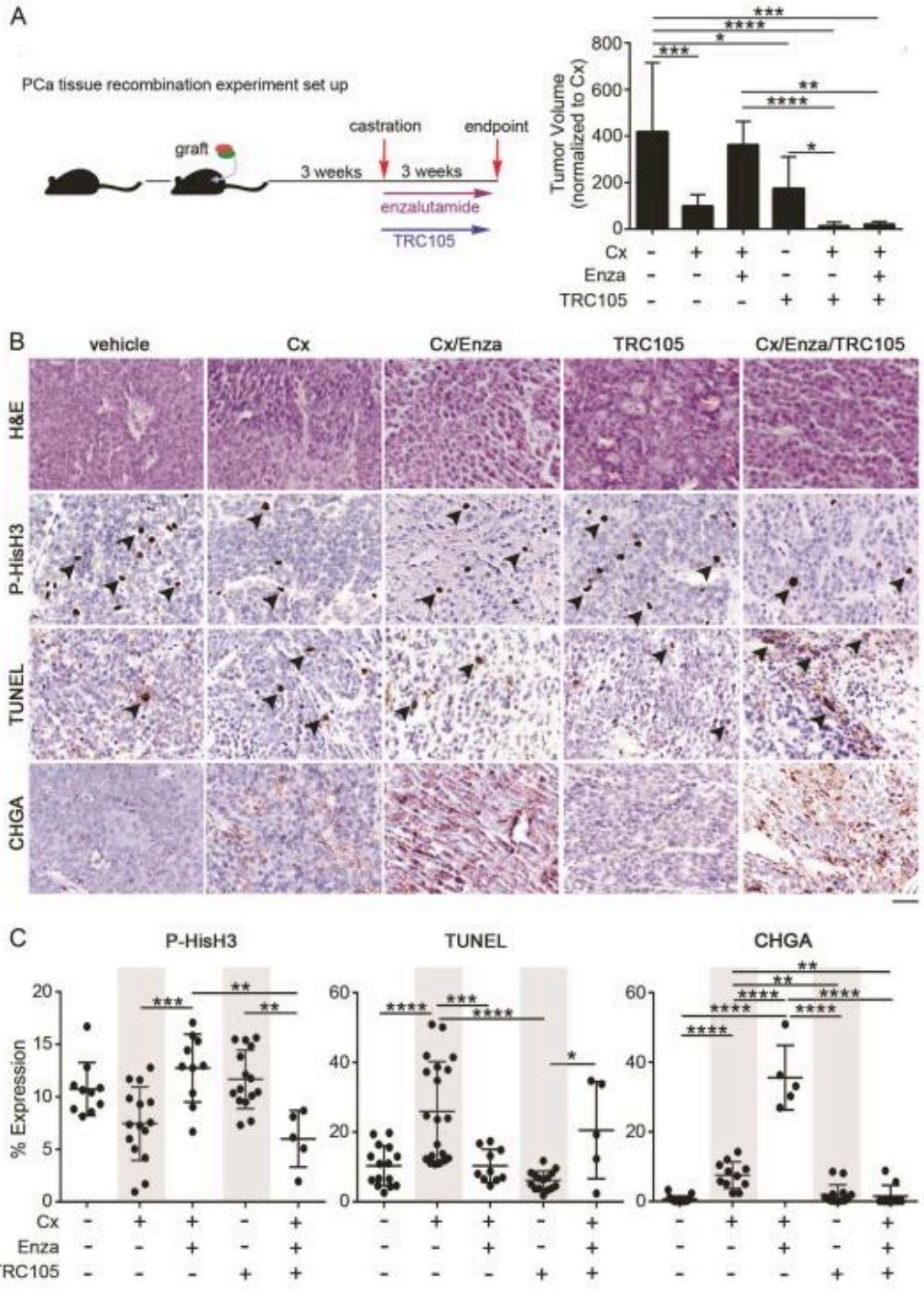


A Pie charts illustrate the relative ratio of the indicated stromal fibroblastic populations based on cell surface expression of the indicated markers: CD90+/CD105+ (blue), CD90+/Stro-1+ (purple), CD90+/CD117+ (red), and CD90− (green), n > 3. ANOVA analysis demonstrates NAF, CAF, and CAFHiP have distinct populations ($p < 0.03$). **B** Scatter plot indicates individual tumor volume (log transformed) for tissue recombinant tumors made up of 22Rv1 epithelia with the indicated fibroblastic populations. n > 4. **C** Histology for representative recombinant tumor sections of 22Rv1 with the indicated fibroblastic populations are shown. H&E staining shows tumor morphology (scale bar represents 64 µm). Ki67 and TUNEL immune localization, with hematoxylin nuclear counterstain (scale bar represents 32 µm), is shown, n > 5. **D** The scatter plot shows quantitation of percent expression for Ki67 immunohistochemical staining, n > 8. **E** The scatter plot shows quantitation of the number of TUNEL positive nuclei per field by immunohistochemical staining, n > 5. For all, error bars are mean ± SD, and p-values of < 0.05, **p < 0.01, ***P < 0.001, ****p < 0.0001).

Source: Kato M et al. Oncogene. 2019;38(5):716-730

Sensitizing Androgen Deprivation Therapy Through CD105 Inhibition

Figure 6. Inhibiting CD105 Can Sensitize Prostate Cancer Androgen-targeted Therapy



A Mice were orthotopically grafted with tissue recombinants of 22Rv1 (a human prostate carcinoma cell line) and CAF. The mice were castrated, treated with TRC105, and/or enzalutamide. Bar graph shows tumor volumes normalized to castrated (Cx) mice. B H&E staining was followed by immune-localization for phosphorylated-histone H3 (PHisH3), TUNEL, and chromogranin A (CHGA). Scale bar represents 32 μm. C The scatter plots show the mitotic (PHis-H3), cell death (TUNEL), and chromogranin A positive staining indexes, mean ± SD, n > 5. For all, error bars are mean ± SD, and p-values of < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001).

Source: Kato M et al. Oncogene. 2019;38(5):716-730

The question arose as to whether or not inhibiting CD105 “re-sensitizes” castrate resistant prostate cancer to androgen deprivation therapy. To test this hypothesis Kato and colleagues utilized an orthotopic castrate-resistant tissue recombinant mouse model comprised of human CAF and 22Rv1 (a human prostate cancer cell line). The tumors were expanded in mice for 3 weeks prior to castration. A subset of mice were treated with enzalutamide, in the presence or absence of TRC105 for an additional 3 weeks to mimic secondary treatment after castration equivalent therapies had failed. TRC105, a human-specific CD105 antibody, was found not to impact host vascularization of xenografts. Castrated mice had reduced tumor volumes compared to controls ($p < 0.001$; Figure 6a). Histologic measure of mitosis by phosphorylated-histone H3 was unchanged, however castration resulted in an expected increase in TUNEL staining ($p < 0.0001$; Figure 6b-c). In this CRPC xenograft model, the castrated mice given enzalutamide had tumor volumes and histologic measures of cell turnover statistically comparable to control intact mice. Mice treated with TRC105 alone had tumors smaller than vehicle ($p < 0.05$), with no notable changes in histology, proliferation, or cell death, compared to control. As patients on enzalutamide are normally at a castrate state, the authors combined castration with enzalutamide and compared the tumors to that generated following the addition of TRC105. Substantially reduced tumor size was found with the addition of TRC105 compared to either control or castrated-enzalutamide treatment alone ($p < 0.001$ and $p < 0.01$, respectively). Castrated mice given TRC105 resulted in the smallest tumor volume compared to control ($p < 0.0001$), with tumors too small to section for reliable histologic analysis. The marked chromogranin A staining associated with ADT (castrated mice given enzalutamide), was reduced by the added administration of TRC105 (p value < 0.0001).

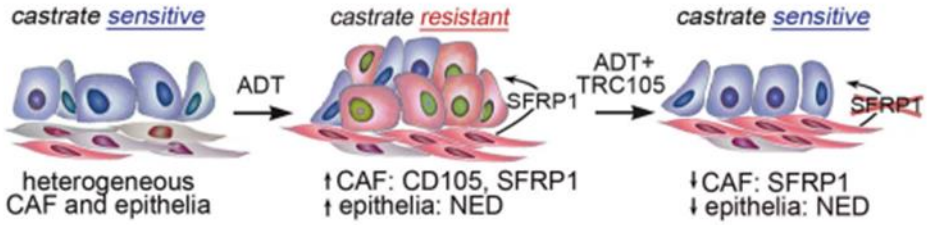
In most patients who are treated for advanced recurrent prostate cancer with androgen-deprivation therapy, disease progression occurs despite effective suppression of serum testosterone. This disease state is called castration-resistant prostate cancer and is associated with increases in levels of serum prostate-specific antigen (PSA), suggesting that the disease continues to be driven by androgen-receptor signaling. Therefore, there is the need to further suppress the androgen axis by blocking androgen synthesis or the androgen receptor. Enzalutamide is a direct androgen receptor inhibitor. The phase 3 PREVAIL trial demonstrated that enzalutamide improved radiographic progression-free survival and overall survival among men with chemotherapy-naïve metastatic castration-resistant prostate cancer. Survival improved by 2 months in castration-resistant prostate cancer (CRPC) patients who had not yet received chemotherapy.[11]

Despite the initial efficacy of ADT many patients develop CRPC with the acquisition of neuroendocrine features by the cancer epithelia.[9] This, however, is at odds with the incidence of the disease because neuroendocrine tumors of the prostate occur in under 1% of patients yet according to Rahul Aggarwal and colleagues the features of neuroendocrine prostate cancer occur in 10-15% of patients.[12] Kato and others identified a stromal CD105-expressing population in cancer associated fibroblasts that can mediate neuroendocrine differentiation and subsequent castration-resistant prostate cancer. The group believed CD105 can serve as a target to restore castrate sensitivity complementing androgen deprivation therapy. They found that stromal CD105 expression was associated with prostatic epithelial neuroendocrine differentiation in patient tissues (Figure 7). Combining androgen-targeted therapy with a CD105 antibody reduced neuroendocrine differentiation and tumor size. This serves as a model for therapy-resistant disease.

[11] Beer TM, Armstrong AJ, Rathkopf DE, *et al.* Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433. doi:10.1056/NEJMoa1405095

[12] Aggarwal RR, Feng FY, Small EJ. Emerging Categories of Disease in Advanced Prostate Cancer and Their Therapeutic Implications. *Oncology (Williston Park)*. 2017;31(6):467-474.

Figure 7. Hypothesis of the Evolution of Prostate Cancer.



Antagonizing the androgen axis increases CD105 and Secreted frizzled-related protein 1 (SFRP) expression with elevated neuroendocrine differentiation. Diagram shows the evolution of prostate cancer stroma and epithelia. Castrate sensitive prostate cancer epithelia (blue top layer of cells) and stromal fibroblasts (bottom elongated layer of gray and CD105+ red cells) are both initially heterogeneous. After treatment with ADT, the epithelia and stroma express more CD105 (red). ADT induces SFRP1 secretion by fibroblasts that signal to the adjacent epithelia to induce neuroendocrine differentiation. The combined treatment with ADT and CD105 inhibition with TRC105 resulted in SFRP1 downregulation and reduced epithelial neuroendocrine differentiation in promoting castrate sensitivity.

Source: Kato M et al. Oncogene. 2019;38(5):716-730

Kato and colleagues identified that CD105/BMP signaling is upregulated in response to ADT using mouse models. Stromal CD105 expression was associated with prostatic epithelial neuroendocrine differentiation in patient tissues. Interestingly the authors discovered that combining androgen-targeted therapy with a CD105 neutralizing antibody markedly reduced neuroendocrine differentiation and resultant tumor size in a 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.[9] The data support the notion that targeting of both stromal and epithelial cell compartments with TRC105 and ADT could provide a better therapeutic outcome for CRPC patients.

Phase 1 Study of Anti-Endoglin (CD105) Antibody TRC105.

Karzai and others at the National Cancer Institute evaluated the antibody known as TRC105, which binds to CD105 (endoglin), in castration-resistant prostate cancer. Patients with mCRPC received escalating doses of TRC105 intravenously using a standard 3 + 3 phase 1 design.

A total of 20 patients were treated. The top dose level studied, 20 mg/kg every 2 weeks, was defined as the maximum tolerated dose. Common adverse effects included infusion-related reaction (90%), low grade headache (67%), anemia (48%), epistaxis (43%) and fever (43%). Fifty percent of the patients had stable disease on study and 40 percent of the patients had declines in prostate specific antigen (PSA). Significant plasma CD105 reduction was observed at the higher dose levels. In an exploratory analysis, vascular endothelial growth factor (VEGF) was increased after treatment with TRC105 and VEGF levels were associated with CD105 reduction.

The authors concluded that TRC105 was tolerated at 20 mg/kg every other week with a safety profile distinct from that of VEGF inhibitors. A significant induction of plasma VEGF was associated with CD105 reduction, suggesting anti-angiogenic activity of TRC105. There appeared to be a correlation of a reduction of CD105 and a decrease in PSA. But overall as a monotherapy, TRC105 has limited therapeutic benefit. Rising VEGF levels may be a compensatory mechanism for TRC105-induced anti-angiogenic activity.[13]

[13] Karzai FH, Apolo AB, Cao L, *et al.* A phase I study of TRC105 anti-endoglin (CD105) antibody in metastatic castration-resistant prostate cancer. *BJU Int*. 2015;116(4):546-555. doi:10.1111/bju.12986,

Hypothesis for Reliable Biomarkers in Prostate Cancer

Drugs such as enzalutamide and abiraterone represent breakthroughs in the treatment of metastatic castration-resistant prostate cancer. Both abrogate androgen signaling. Enzalutamide (XTANDI) is a potent inhibitor of androgen receptor binding, yet it also inhibits androgen receptor translocation and DNA binding. Abiraterone (ZYTIGA) is different from enzalutamide in that it blocks the CYP17A enzyme, which is required for androgen synthesis. Independently both drugs obtained FDA approval because they improve patient survival. However, with respect to PSA levels, approximately 20%-40% of patients have no response to these drugs. Further, in patients who initially have a response to enzalutamide or abiraterone, virtually all eventually acquire secondary resistance. One explanation for the resistance to both agents may involve the presence of androgen-receptor splice variants.[14,15] These alternatively spliced variants encode a truncated androgen-receptor protein that lacks the C-terminal ligand-binding domain but retains the transactivating N-terminal domain. Although the resultant truncated proteins are unable to bind ligand, they are constitutively active as transcription factors and capable of promoting activation of target genes.

Multiple mechanisms, such as androgen receptor (AR) amplification, activating mutations, deletions, gene fusions, and RNA splice variants lead to resistance to androgen receptor signaling inhibition. Antonarakis and colleagues investigated splice variant 7 (AR-V7) in part because it was the only known variant encoding a functional protein product that is detectable in clinical specimens.[16] This domain is the target of the antiandrogen therapies such enzalutamide and abiraterone. Despite the absence of ligand binding, the receptor isoform remains constitutively active as a transcription factor. Antonarakis and colleagues from Johns Hopkins and the University of Texas at San Antonio hypothesized that detection of AR-V7 in circulating tumor cells from men with advanced prostate cancer would be associated with resistance to enzalutamide and abiraterone.[16]

Using a quantitative (reverse transcriptase polymerase chain reaction) assay, Antonarakis and colleagues evaluated AR-V7 in circulating tumor cells from patients having mCRPC who were treated with antiandrogen therapy. A total of 31 enzalutamide-treated patients and 31 abiraterone-treated patients were enrolled, of whom 39% and 19%, respectively, had detectable AR-V7 in circulating tumor cells. Among those receiving enzalutamide, AR-V7–positive patients had lower PSA response rates than AR-V7–negative patients (0% vs. 53%, P=0.004) and shorter PSA progression–free survival (median, 1.4 months vs. 6.0 months; P<0.001; Figure 8), clinical or radiographic progression–free survival (median, 2.1 months vs. 6.1 months; P<0.001; Figure 8), and overall survival (median, 5.5 months vs. not reached; P=0.002, Figure 9). Similarly, among men receiving abiraterone, AR-V7–positive patients had lower PSA response rates than AR-V7–negative patients (0% vs. 68%, P=0.004), shorter PSA progression–free survival (median, 1.3 months vs. not reached; P<0.001; Figure 8), clinical or radiographic progression–free survival (median, 2.3 months vs. not reached; P<0.001; Figure 8), and overall survival (median, 10.6 months vs. not reached, P=0.006, Figure 9).

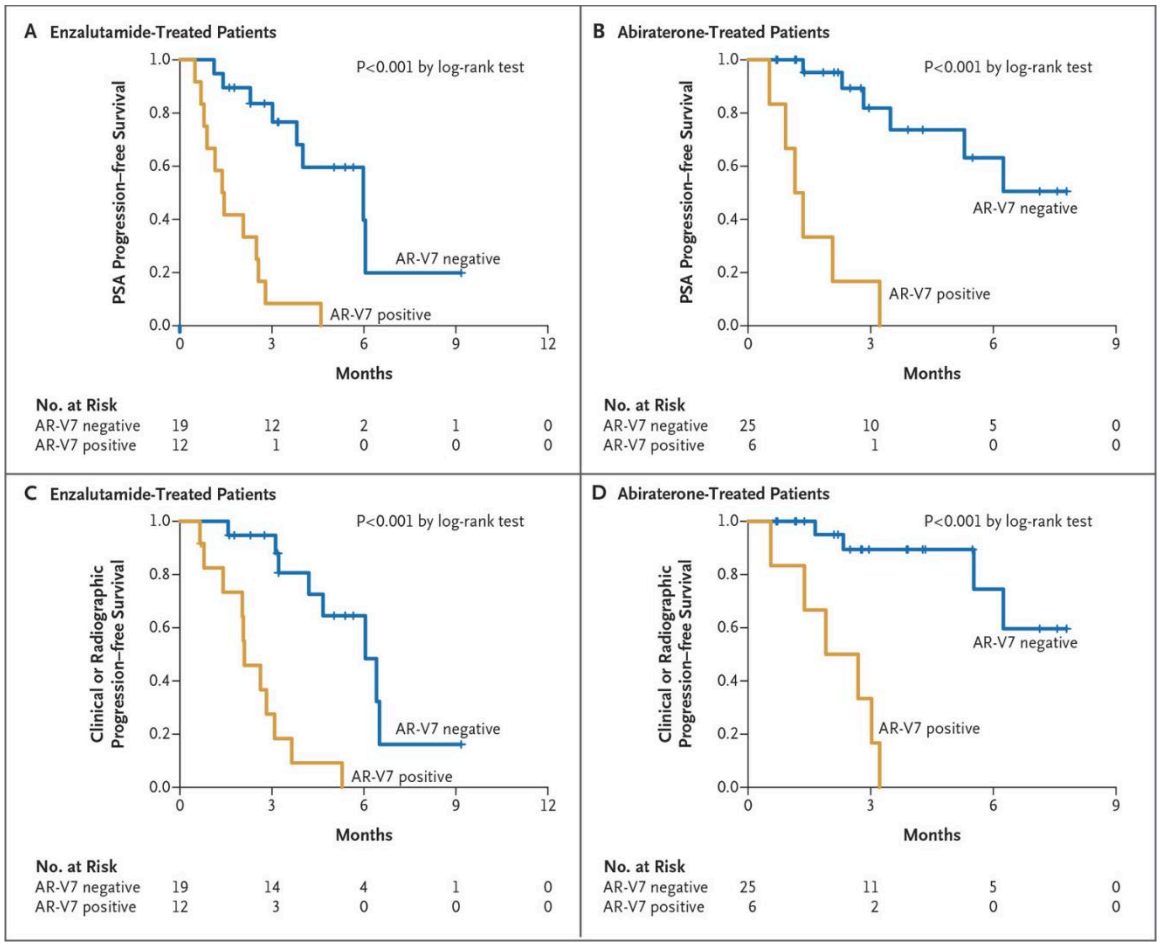
The association between AR-V7 detection and therapeutic resistance was maintained after adjustment for expression of full-length androgen receptor messenger RNA.[16]

The authors conclude that detection of AR-V7 in circulating tumor cells from patients with castration-resistant prostate cancer may be associated with resistance to enzalutamide and abiraterone.[16]

[14] Nadiminty N, Tummala R, Liu C, *et al.* NF-κB2/p52 induces resistance to enzalutamide in prostate cancer: role of androgen receptor and its variants. *Mol Cancer Ther*. 2013;12(8):1629-1637. doi:10.1158/1535-7163.MCT-13-0027

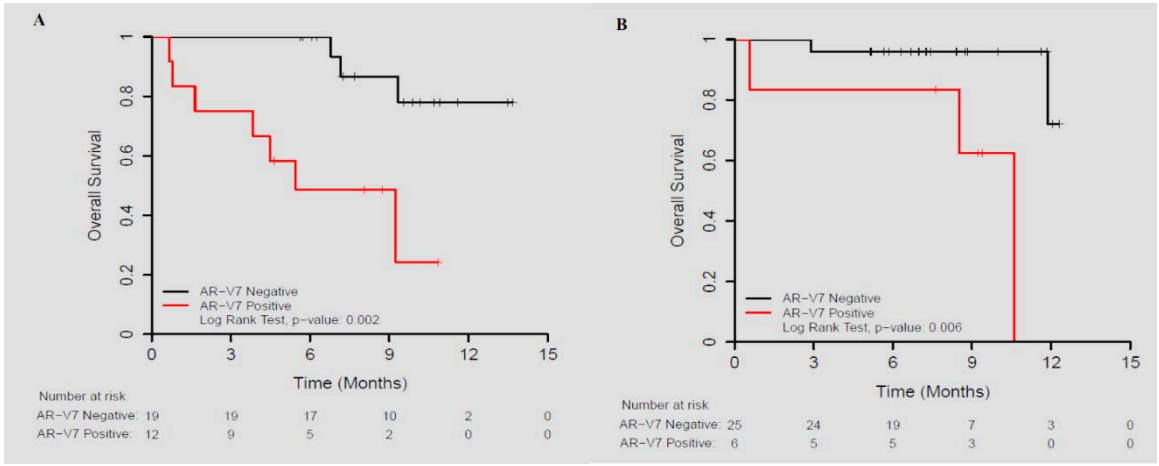
[15] Mostaghel EA, Marck BT, Plymate SR, *et al.* Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. *Clin Cancer Res*. 2011;17(18):5913-5925. doi:10.1158/1078-0432.CCR-11-0728

Figure 8. Kaplan–Meier Analysis of PSA Progression–free Survival and Clinical or Radiographic Progression–free Survival According to AR-V7 Status



Source: Antonarakis ES et al. N Engl J Med. 2014;371(11):1028-1038

Figure 9. Overall survival analysis stratified by AR-V7 status in patients treated with enzalutamide (A) and abiraterone (B)



Source: Antonarakis ES et al. N Engl J Med. 2014;371(11):1028-1038

This variant is associated with 40% androgen receptor inhibitor therapy resistance.[16] Roughly that 20-40% of prostate cancer patients do not respond to androgen signaling inhibitors from the start, and nearly all fail therapy, attributed to the heterogenous nature of prostate cancer tumors. Because ENV105 does not target the androgen receptor as many prostate cancer therapies do, it provides a novel means of addressing castrate resistance. In terms of biomarkers, Kairos identified 3 that suggest responsivity to combinations of androgen signaling inhibitors and ENV105. None of these possible biomarkers are traditional NEPC (neuroendoctine prostate cancer) markers. But as we have stated earlier, Kairos scientists have received NIH funding to more comprehensively examine a broader set of markers in a prospective manner through the ongoing trial. As for AR-V7, it should be noted that it is downregulated in nearly all patients receiving ENV105,[17] but that did not turn out to be a dominant marker for predicting response. This appears to be a testament to the multifactorial mechanism of resistance.

It is also important to note that ENV105 (blocking CD105) does not only limit neuroendocrine differentiation, it also prevents the RNA splicing of the androgen receptor to a dominant active variant (AR-V7).[17]

A subsequent supposition by the Bhowmick group at Cedars Sinai is that binding of CD105 with carotuximab can turn AR-V7+ patients into AR-V7 negative patients.

Does AR-V7 Play a Role in Prostatic Carcinoma Associated Fibroblasts

Smith and others hypothesized that AR-V7 may have a role in prostatic carcinoma – associated fibroblasts (CAFs).[17] Transforming growth factor b (TGF-β) signaling is thought to be a regulator of prostate cancer development, progression, and castration resistance. TGF-β signaling in fibroblasts modulates the growth and oncogenic potential of adjacent epithelia in selected tissues.[18]

TGF-β was found to be elevated in response to castration and indicative of prostate cancer epithelial cell death. The authors have previously reported that inhibition of TGF-β signaling through epigenetic silencing of TGF-β receptor type 2 (*Tgfbr2*) in prostatic CAF potentiates tumor progression and castrate resistance through paracrine (activity in the vicinity) signaling mechanisms.[17] Separately another mechanism behind limiting TGF-β signaling is through expression of CD105 (endoglin). Importantly, CD105 simultaneously inhibits TGF-β signaling while promoting bone morphogenetic downstream signaling.

Because CD105 is expressed on cancer epithelia, immune cells and fibroblasts, the notion of inhibiting the receptor with an antibody (carotuximab or TRC105) had previously been tested as a monotherapy in mouse models and in patients with CRPC. TRC105 does not have an active Fc with ADCC or antibody-dependent cellular cytotoxicity activity. But there was limited therapeutic benefit in animals or humans.[9,13] However, Smith and colleagues, having observed that androgen receptor signaling inhibition found that CD105 was upregulated by both prostate cancer epithelia and cancer-associated fibroblasts (CAF) determined that TRC105/carotuximab in combination with castration or enzalutamide treatment significantly reduced tumor progression in mouse models of CRPC. AR-V7 expression was dependent on CD105 in both prostate cancer stromal fibroblasts and prostate cancer epithelia.[17]

Therapies to target androgen signaling become limited as patients continue to progress through treatment. The standard of care for those who progress becoming resistant to androgen signaling inhibition is chemotherapy. But there is toxicity. Radionuclide (such as lutetium Lu 177 vipivotide tetraxetan or Pluvicto) and antibody dependent conjugates (ADCs). Perhaps a more palliative alternative are the pre-clinical findings of Smith and colleagues in which the addition of carotuximab in metastatic CRPC patients rescues resistance to enzalutamide or abiraterone.

[16] Antonarakis ES, Lu C, Wang H, *et al.* AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*. 2014;371(11):1028-1038. doi:10.1056/NEJMoa1315815

[17] Smith BN, Mishra R, Billet S, *et al.* Antagonizing CD105 and androgen receptor to target stromal-epithelial interactions for clinical benefit. *Mol Ther*. 2023;31(1):78-89. doi:10.1016/j.ymthe.2022.08.019

[18] Bhowmick NA, Chytil A, Plieth D, *et al.* TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science*. 2004;303(5659):848-851. doi:10.1126/science.1090922

Phase 1/2 Androgen Receptor Inhibitors Plus Carotuximab in CRPC Patients

Patients experiencing disease progression while on androgen receptor signaling inhibitors were enrolled. Progression was exhibited as a rise in serum PSA concentration (biochemical progression) as well as radiographic progression while taking abiraterone or enzalutamide. Patients on active therapy with abiraterone or enzalutamide were required to hold treatment for 2 weeks prior to starting combination therapy.

Figure 10. Summary of CRPC Patients Treated with AR Signaling Inhibitors and Carotuximab

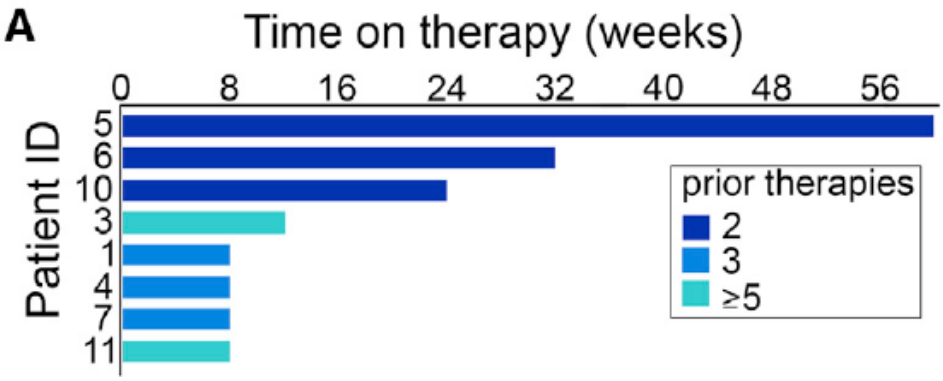
Patient ID	Age (years)	Baseline PSA (ng/mL)	Previous lines of therapy	Previous ARSI	Previous taxane	Best response	PFS (weeks)	Comments
1	72	38.8	3	A/E	no	PD	7	
2	70	728.3	2	A/E	no	NA	NA	unable to complete loading dose
3	57	244.4	5+	A/E	yes	SD	12	PSA decline to 175.3 ng/mL
4	71	11.8	2	A/E	no	PD	7	PSA decline following d/c carotuximab while on enzalutamide
5	72	8.8	2	A/E	no	SD	66	
6	73	2.2	2	E	yes	SD	16	clinical progression at 32 weeks
7	79	182.6	3	A/E	no	PD	7	
8	74	192.3	4	A/E	no	NA		unable to complete 2 weeks
9	75	123.1	5+	A/E	yes	PD	7	
10	74	5.9	2	A	no	SD	60	
11	60	70.5	5	A/E	yes	PD	7	

Prior androgen receptor signaling inhibitor therapy included abiraterone (A) and/or enzalutamide (E). Combination therapy achieved progressive disease (PD), stable disease (SD), or not available (NA). The weeks of on-treatment progression-free disease (PFS) are indicated. The patients enrolled in the NCT03418324 study had multiple lines of prior therapy inclusive of androgen receptor signaling inhibitors and taxanes, having progression on either abiraterone or enzalutamide. There were variable responses to the open-label combination therapy strategy of either abiraterone or enzalutamide with carotuximab. Radiographic PFS >8 weeks was a measure response with stable disease.

Source: Smith BN et al. Mol Ther. 2023;31(1):78-89.

It should be noted that at the time of this study the goal was to enroll up to 40 patients. However, Tracon Pharmaceuticals, which owned carotuximab at the time abandoned development of the antibody as there was no efficacy in kidney cancer and soft tissue sarcoma. However, at the time of Tracon's decision 11 CRCP patients had been accrued. Several patients had up to five clinical interventions prior to enrollment. Two patients had rapid disease progression and were not assessable to treatment with carotuximab (Figure 10). Of the accessible patients, the PFS rate at 8 weeks was 44%. Using RECIST 1.1 and PCWG3 criteria, median radiographic PFS was 12 weeks (range 7-66 weeks) (Figure 10). One observation was that the number of previous lines of therapy affected PFS (Figure 11). That is patients with two lines of therapy experienced clinical progression at an average of 52 weeks (range 32-66 weeks, Figure 10). One patient with >5 lines of therapy including chemotherapy with docetaxel and radiotherapy for brain metastases, experienced a 28% decrease in serum PSA and remained on therapy for 12 weeks. The patient progressed both clinically and radiographically from central nervous system disease (Figure 10). Two patients who remained on therapy for 66 and 60 weeks, respectively had only two lines of therapy and no prior taxane chemotherapy (Figure 10). One of these patients experienced clinical stability for 3 months after stopping combination therapy. His PSA dropped from 18.5 ng/ml to 4.7 ng/ml before rising to 57.3 ng/ml. The patient at that time decided to have treatment with a non-steroidal anti-androgen. His PSA declined 90% and he remained on therapy for 9 months (Figure 10). Smith and colleagues reported that after stopping carotumixab therapy, the patient became taxane responsive and experienced a substantial PSA decline on chemotherapy (57% decrease on PFS for 8 months) despite demonstrating docetaxel resistance previously.

Figure 11. CRPC Patients Treated with Androgen Signaling Inhibitors and Carotuximab.



A 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.

Source: Smith BN et al. Mol Ther. 2023;31(1):78-89.

To put these data into perspective a PARP inhibitor, Rucaparib (Rubraca) had a 58% objective response rate in BRACA 1 mutant patients. BRACA1 mutant patients are less than 10% of the prostate cancer population. Pluvicto (lutetium Lu 177 vipivotide tetraxetan), a radionucleotide, given in combination with hormone therapy had an 8.7-month median radiographic PFS. In the phase 3 trial the 6 week objective response rate was 51% (52.7% grade 3 toxicity). Apalutamide (Erleada) in combination with androgen deprivation therapy has a 22% 12-week biochemical PFS rate. The Grade 3 toxicity rate was 45.1%.

Next Steps

Kairos believes ENV105 to be suited for those patients failing first line AR inhibition, which happens in about 18 months from the start of hormone therapy. By giving ENV105 with second line hormone therapy one could potentially extend the current median 2 months of efficacy to something significantly longer.[17] Both prostate and bone marrow fibroblasts have an elevation of CD105 upon AR inhibition. The stromal heterogeneity is present even in the primary tumor in treatment naïve patients. In fact, therapy can enrich certain populations to reduce some heterogeneity.

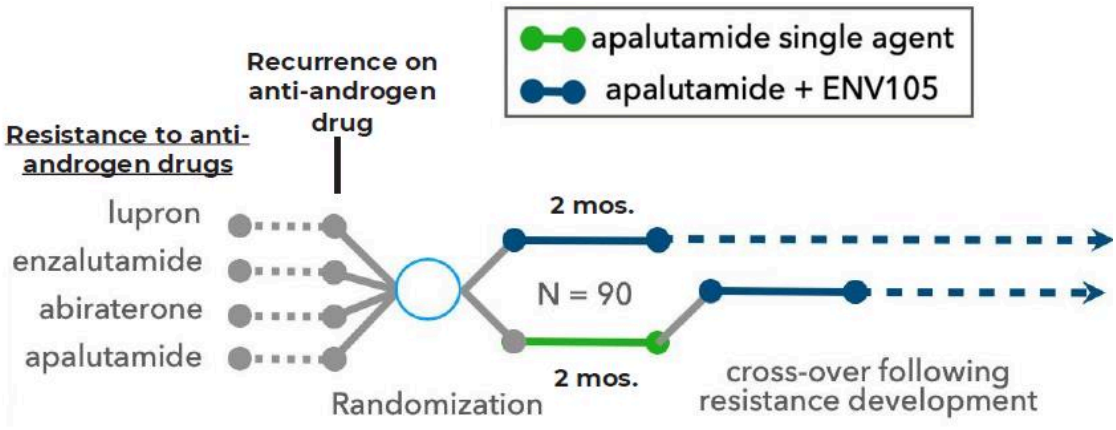
A phase 2 study began to enroll in 2023 with a goal to enroll n=90 subjects having castration-resistant prostate cancer. The trial is enrolling at Cedars Sinai with two other sites, City of Hope and the Huntsman Cancer Center in Salt Lake City, who per clinicaltrials.gov have not yet begun enrolling patients.

This is an open-label, multi-site study of apalutamide with carotuximab in patients who have progressed on androgen receptor signaling inhibitor (ARSI) therapy (Figure 12). This study will begin with a safety assessment in the first 10 subjects (part 1: Safety Lead-in). If the combination is deemed safe, the trial will proceed to the Phase 2 stage. The purpose of this study is to compare progression free survival (PFS) between patients receiving apalutamide and apalutamide + carotuximab using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and Prostate Cancer Working Group 3 (PCWG3). The secondary objectives are to describe adverse events related to the intervention, overall response rate (ORR), proportion of patients resistant to apalutamide that benefit from the addition of carotuximab, and to determine the ORR, radiographic PFS, and biochemical PFS in the overall population.

All prostate cancer drugs approved in the past 5 years have been based on improvement in progression free survival (PFS). Kairos believes a 4-month PFS would be the bar to cross, as this would be double that of the median of current standard of care for CRPC subjects. Based on data to date, Kairos are highly confident this and subsequent trials would suggest a 4-month hurdle can be surpassed. We anticipate seeing interim data in Q1 2025.

Earlier data from prostate cancer patients has seen triple-digit PSA drops, but this is not the sole measure of efficacy. The current trial is designed to adhere to the standard RECIST v1.1 and PCWG3 consensus criteria, which includes radiographic criteria. Visual tumor response (partial or complete) is important. As stated earlier, the FDA does not require OS change to approve prostate cancer drugs, but patients will be followed for changes in overall survival.

Figure 12. Phase 2 Trial- Enrolling



Source: Kairos Corporate Deck, December 2024

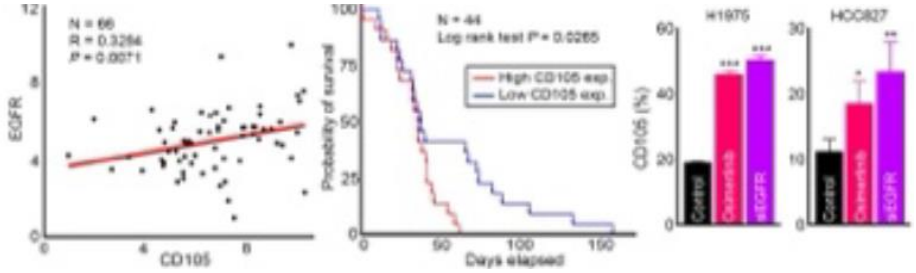
ENV105/TRC105 is present in circulation 2 weeks after infusion and detected even a month out. Thus, after 4 months of infusions every 2 weeks, Kairos will drop infusions to once-a-month in combination with daily apalutamide (oral). This has been shown to limit toxicity (nose bleeds and fatigue).

ENV105 in EGFR-Refractory Non-Small Cell Lung Cancer

Approximately 15-20% of non-small cell lung cancer (NSCLC) patients develop mutations in the epidermal growth factor receptor (EGFR) that can be targeted by tyrosine kinase inhibitors (TKIs).[19] Last year this amounted to roughly 45,000 EGFR mutated lung cancers. Osimertinib, a third generation TKI, has emerged as the standard of care for patients diagnosed with EGFR driven NSCLC.[20,21,22] Activating mutations in the epidermal growth factor receptor (EGFR) gene in NSCLC patients are associated with clinical benefit in the metastatic and adjuvant settings when treated with EGFR inhibitors, such as osimertinib. Despite its dramatic efficacy, most patients are partial responders and refractive disease leaves limited treatment options. In fact the objective of M. Thiruvalluvan and colleagues at Cedars Sinai was to dissect the mechanism of Osimertinib resistance in EGFR mutant NSCLC models and to identify a means of resensitization. Imaging mass cytometric analysis of 76 NSCLC patients demonstrated EGFR expression was inversely correlated to CD105 membrane expression.[23] Osimertinib has been shown to increase CD105 expression on the cell surface.

In the *in vitro* experiments by Thiruvalluvan, 76 tumors patients with NSCLC treated at Cedars-Sinai Medical Center were evaluated and used to generate a tissue microarray (TMA). The TMA was subjected to imaging mass cytometry where 66 specimens were assessable and had detectible signal for EGFR and CD105.

Figure 13. Correlation of CD105 expression to EGFR expression in treatment naive NSCLC patients



Left Panel. Spearman's correlation of EGFR and CD105 expression from the tissue samples from 66 NSCLC patients demonstrate a significant positive correlation. *Middle Panel*. Kaplan-Meier plot of logistic regression analysis of median overall survival based on CD105 expression status. *Right Panel*. FACS analysis of H1975 and HCC827 cells for cell surface CD105 expression were measured following treatment with vehicle, osimertinib and EGFR siRNA knockdown. *P < 0.05, **P < 0.01, ***P < 0.001.

Source: Thiruvalluvan M et al. Cancer Res 15 March 2024; 84 (6_Supplement): 4759

In Figure 14. the EGFR mutant cell lines H1975 and HCC829 were grafted on NSG mice. Mice were then treated with Osimertinib alone or Osimertinib with carotuximab. Combination therapy of carotuximab and osimertinib resulted in significantly reduced tumor expansion compared to mice treated with either drug alone. Inhibition of CD105 with carotuximab can overcome resistance to osimertinib and inhibit/reduce NSCLC tumor progression.

[19] Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res*. 2015;5(9):2892-2911.

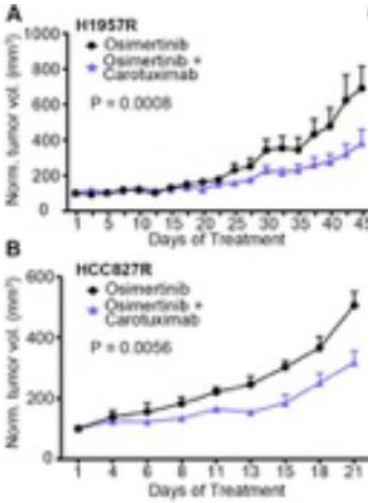
[20] Soria JC, Ohe Y, Vansteenkiste J, *et al.* Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(2):113-125. doi:10.1056/NEJMoa1713137

[21] Jänne PA, Yang JC, Kim DW, *et al.* AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1689-1699. doi:10.1056/NEJMoa1411817

[22] Wu YL, Tsuboi M, He J, *et al.* Osimertinib in Resected *EGFR*-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020;383(18):1711-1723. doi:10.1056/NEJMoa2027071

[23] Thiruvalluvan M, Billet S, Liu Z. Abstract 4759: Targeting slow-cycling persisters in EGFR mutant non-small cell lung cancer. *Cancer Res* 15 March 2024; 84 (6_Supplement): 4759. https://doi.org/10.1158/1538-7445.AM2024-4759

Figure 14. Carotuximab reduces size of Osimertinib resistant tumors



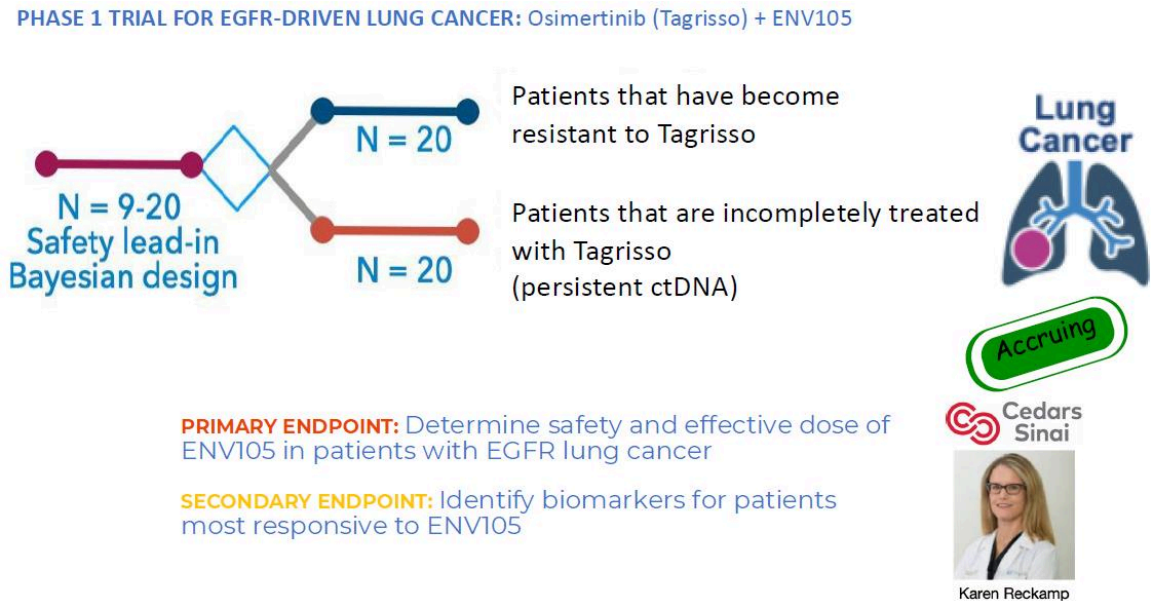
(A) H1975R cells were subcutaneously grafted into NSG mice (n=6) and were administered osimertinib (1 mg/kg) or osimertinib in combination with carotuximab (1 mg/kg) over a period of 46 days. Tumor volume fold change was normalized to the first dose of osimertinib. (B) HCC827R cells were xenografted into NSG mice (n=6) and were administered osimertinib (5 mg/kg) or osimertinib in combination with carotuximab (1 mg/kg) over a period of 46 days. Tumor volume fold change was normalized to the first dose of osimertinib.

Source: Thiruvalluvan M et al. Cancer Res 15 March 2024; 84 (6_Supplement): 4759

Osimertinib effectively treats EGFR-mutant NSCLC by slowing disease progression, though resistance inevitably develops. The authors found EGFR and CD10 5 receptor expression were directly correlated in treatment-naïve patients, but they also found that elevated CD105 expression is linked to shorter OS in patients receiving TKI therapy. Inhibition of EGFR signaling increases CD105 and BMP ligands expression. Osimertinib-resistant cell lines show expected EGFR bypass signaling mechanisms and increased mutational load. The authors believe the data supports a novel synthetic lethality treatment strategy.

Kairos is testing carotuximab in EGFR+ NSCLC. The trial design is noted in Figure 15. According to clinicaltrials.gov 5 clinical sites are recruiting patients.

Figure 15. Phase 1 Study in EGFR Mutated Non-Small Cell Lung Cancer



Source. Kairos Corporate Deck December 2024

Appendix

Prostate Cancer and Prostate Cancer Treatment: Comments from The National Cancer Institute

Androgens

Androgens (male sex hormones) are a class of hormones that control the development and maintenance of male characteristics. The most abundant androgens in men are testosterone and dihydrotestosterone. Androgens are required for normal growth and function of the prostate. The prostate is a gland in the male reproductive system that helps make semen. Androgens are also necessary for prostate cancers to grow.[24] Once activated, the androgen receptor stimulates the expression of specific genes that cause prostate cells to grow.[25] Almost all testosterone is produced in the testicles, though a small amount is produced by the adrenal glands. Although prostate cells do not normally make testosterone, some prostate cancer cells acquire the ability to do so.[26]

Hormone therapy and prostate cancer

Prostate cancers, early in their development, need androgens to grow. Hormone therapies, which are treatments that decrease androgen levels or block androgen action, can inhibit the growth of prostate cancers. Those cancers are called castration-sensitive prostate cancer. Such cancers may also be described as being androgen dependent, androgen sensitive, or hormone sensitive.

Most prostate cancers eventually stop responding to hormone therapy and become castration resistant (CRPC). That is, they continue to grow even when androgen levels in the body are extremely low or undetectable. In the past, these tumors were also called hormone resistant, androgen independent, or hormone refractory.

Types of hormone therapy used for prostate cancer

Hormone therapy for prostate cancer can block the production or use of androgens.[27] Currently available treatments can do so in several ways:

- Reducing androgen production by the testicles
- Blocking the action of androgens throughout the body
- Blocking androgen production (synthesis) throughout the body including by prostate cancer cells

Treatments that reduce androgen production by the testicles are the most commonly used hormone therapies for prostate cancer and the first type of hormone therapy that most people with prostate cancer receive. This form of hormone therapy, which is called androgen deprivation therapy, or ADT, includes:

- Orchiectomy, a surgical procedure to remove both testicles. Removal of the testicles, called surgical castration, can reduce the level of testosterone in the blood by 90% to 95%.[28]
- Luteinizing hormone-releasing hormone (LHRH) agonists prevent the pituitary gland from secreting luteinizing hormone. LHRH agonists (a.k.a. LHRH analogs) are synthetic proteins that are structurally similar to LHRH and bind to LHRH receptors in the pituitary gland.

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[25] Hååg P, Bektic J, Bartsch G, Klocker H, Eder IE. Androgen receptor down regulation by small interference RNA induces cell growth inhibition in androgen sensitive as well as in androgen independent prostate cancer cells. *J Steroid Biochem Mol Biol*. 2005;96(3-4):251-258. doi:10.1016/j.jsbmb.2005.04.029

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Normally, when androgen levels in the body are low, the hypothalamus releases LHRH. This stimulates the pituitary gland to produce luteinizing hormone, which in turn stimulates the testicles to produce androgens. LHRH agonists, like the body's own LHRH, initially stimulate the production of luteinizing hormone. However, the continued presence of high levels of LHRH agonists actually causes the pituitary gland to stop producing luteinizing hormone. As a result, the testicles are not stimulated to produce androgens.

Treatment with an LHRH agonist is called medical castration or chemical castration. But unlike surgical castration (orchiectomy), medical castration is reversible. Once treatment is stopped, androgen production usually resumes.

LHRH agonists are given by injection or are implanted under the skin. Approved LHRH agonists in the United States include leuprolide (Lupron Depot, Eligard, Camcevi), goserelin (Zoladex), and triptorelin (Trelstar).

When patients receive an LHRH agonist for the first time, they may experience a phenomenon called "testosterone flare." This is a temporary increase in testosterone level that occurs because LHRH agonists briefly cause the pituitary gland to secrete extra luteinizing hormone before blocking its release. The flare may worsen clinical symptoms (such as bone pain, ureter or bladder outlet obstruction, and spinal cord compression).

LHRH antagonists are another form of medical castration. LHRH antagonists prevent LHRH from binding to its receptors in the pituitary gland. This in turn prevents the secretion of luteinizing hormone, which stops the testicles from producing androgens. Unlike LHRH agonists, LHRH antagonists do not cause a testosterone flare.

Approved LHRH antagonists in the United States include degarelix (Firmagon), which is given by injection, and relugolix (Orgovyx), which is an oral pill.

Treatments that block the action of androgens in the body are called antiandrogen therapies, androgen receptor blockers, or androgen receptor antagonists. Such treatments work by competing with androgens for binding to androgen receptors. By keeping androgens from binding to androgen receptors, these treatments reduce the ability of androgens to promote prostate cancer cell growth.

Androgen receptor blockers are typically used together with ADT (orchiectomy or an LHRH agonist) because the combination both reduces androgen levels and keeps any remaining androgen from binding to androgen receptors. The combination is often referred to as combined androgen blockade, complete androgen blockade, maximal androgen blockade, or total androgen blockade. In addition to being used as hormone therapy for prostate cancer, androgen receptor blockers are sometimes used for a few weeks at the start of ADT to prevent testosterone flares.

Androgen receptor blockers that are approved in the United States to treat prostate cancer include the "first-generation" drugs flutamide, bicalutamide (Casodex), and nilutamide (Nilandron), and the "second-generation" drugs enzalutamide (Xtandi), apalutamide (Erleada), and darolutamide (Nubeqa). The second-generation drugs bind to and block the androgen receptor more strongly and specifically than the first-generation drugs.[29]

Darolutamide is the only androgen receptor blocker that does not cross the blood-brain barrier in humans, which may result in fewer central nervous system–related side effects. Androgen receptor blockers are given as pills to be swallowed.

Treatments that block the production of androgens throughout the body are known as androgen synthesis inhibitors. Like ADT, androgen synthesis inhibitors prevent androgen production by the testicles. But unlike ADT they also prevent androgen production by the adrenal glands and prostate cancer cells. Even though only small amounts of androgens are produced outside the testicles, the low levels that are still produced can be enough to support the growth of some prostate cancers.

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Androgen synthesis inhibitors lower testosterone levels to a greater extent than any other known treatment. They do so by inhibiting an enzyme called CYP17. This enzyme, which is found in testicular, adrenal, and prostate tumor tissues, is necessary for the body to produce testosterone.

Androgen synthesis inhibitors approved in the United States include abiraterone (Yonsa, Zytiga) and ketoconazole. Both are given as pills to be swallowed.

Abiraterone is used in combination with prednisone to treat metastatic prostate cancer, both castration-sensitive and castration-resistant. Ketoconazole is approved for indications other than prostate cancer but is sometimes used off-label as second-line treatment for CRPC, although such use is rare given the availability of second-generation androgen receptor blockers.

Hormone Therapy for Castration-sensitive Prostate Cancer

Hormone therapy may be used in several ways to treat castration-sensitive prostate cancer, including for early-stage prostate cancer with an intermediate or high risk of recurrence. Men who are having radiation therapy to treat early-stage prostate cancer that has an unfavorable intermediate or high risk of recurrence often receive ADT as well. And ADT may be used after prostatectomy in men who have high-risk node-positive disease.[30,31]

Relapsed/recurrent prostate cancer

Hormone therapy is often used alone for people who have a recurrence of prostate cancer after earlier treatment with radiation or surgery. Hormone therapy is standard treatment for those who have a symptomatic recurrence (as documented by CT, MRI, PSMA PET scan, or bone scan) and may also be recommended for some people who have a "biochemical recurrence" (a rise in prostate-specific antigen (PSA) level after treatment with surgery or radiation), especially if the PSA level is rising rapidly.

Advanced or metastatic prostate cancer

For many years, ADT monotherapy was the standard treatment for men who, at the time of their initial prostate cancer diagnosis, are found to have castration-sensitive metastatic disease.[32] Now, such men are treated with ADT plus another type of hormone therapy (abiraterone, enzalutamide, or apalutamide) or ADT plus the chemotherapy docetaxel (Taxotere) and a second-generation androgen receptor blocker, such as abiraterone or darolutamide. Some of these men, especially those with extensive metastases, may be treated with ADT plus chemotherapy plus another type of hormone therapy.[33]

Although hormone therapy can delay progression of metastatic disease and may extend survival, it can also have side effects.

Palliation of symptoms

Hormone therapy is sometimes used alone for palliation or prevention of local symptoms in men with localized prostate cancer who are not candidates for surgery or radiation therapy.[34] Such men include those with a limited life expectancy, those with locally advanced tumors, and/or those with other serious health conditions.

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[33] Fizazi K, Foulon S, Carles J, *et al.* Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet*. 2022;399(10336):1695-1707. doi:10.1016/S0140-6736(22)00367-1

[34] Studer UE, Whelan P, Albrecht W, *et al.* Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol*. 2006;24(12):1868-1876. doi:10.1200/JCO.2005.04.7423

Hormone therapy duration

There is no way to predict the duration of effectiveness of hormone therapy in suppressing the growth of any individual man's prostate cancer. Therefore, men who take hormone therapy for more than a few months are regularly tested to determine the level of serum PSA. An increase in PSA level may indicate that a man's cancer has started growing again or become resistant to the hormone therapy that is currently being used.

CRPC treatment

- Complete androgen blockade—that is, androgen deprivation therapy plus an androgen receptor blocker (flutamide, bicalutamide, nilutamide, apalutamide, darolutamide, or enzalutamide).
- Androgen synthesis inhibition with abiraterone.
- Chemotherapy, most commonly with docetaxel. Another chemotherapy drug, cabazitaxel (Jevtana), is approved for the treatment of metastatic CRPC that was previously treated with docetaxel.
- Radiopharmaceuticals, including radium-223 dichloride (Xofigo) and lutetium Lu-177 vipivotide tetraxetan (Pluvicto). Radium-223 collects in areas of bone that are undergoing increased turnover (bone resorption coupled with bone formation), such as where bone metastases are forming, and gives off radiation that kills cancer cells. Lutetium Lu-177 vipivotide tetraxetan targets and binds to prostate cells and delivers radiation that kills them.
- PARP inhibitors include rucaparib (Rubraca), olaparib (Lynparza), talazoparib (Talzenna), and niraparib in combination with abiraterone (Akeega) are approved to treat metastatic CRPC that have certain genetic changes that disrupt DNA repair in the cancer cells
- Immunotherapy using a cell-based vaccine called sipuleucel-T (Provenge). This vaccine uses the patient's own immune cells to fight metastatic prostate cancer that has few or no symptoms.

People with CRPC who receive these treatments will continue to receive ADT (e.g., an LHRH agonist) to keep testosterone levels low, because an increase in testosterone could lead to tumor progression.[12]

Side effects of ADT

Because androgens affect many other organs besides the prostate, ADT can have a wide range of side effects,[32] including:

- loss of interest in sex (lowered libido)
- erectile dysfunction
- hot flashes
- loss of bone density
- bone fractures
- loss of muscle mass and physical strength
- changes in blood lipids
- insulin resistance
- weight gain
- mood swings
- fatigue
- growth of breast tissue (gynecomastia)

Antiandrogens can cause diarrhea, breast tenderness, nausea, hot flashes, loss of libido, and erectile dysfunction. The antiandrogen flutamide may damage the liver, and enzalutamide and apalutamide may cause fractures. Darolutamide may avoid some central nervous system–related side effects seen with enzalutamide and apalutamide, such as seizures and falls.

Androgen synthesis inhibitors can cause diarrhea, itching and rashes, fatigue, erectile dysfunction (with long-term use), and, potentially, liver damage.

Market Opportunity

Prostate Cancer

Kairos believes ENV105 to be suited for mCRPC patients who are failing first line androgen receptor inhibition, which happens in about 18 months from the start of hormone therapy. By giving ENV105 with second line hormone therapy one could potentially extend the current median 2 months of efficacy to something that is significantly longer.[17] Early data suggest this is possible.

In the US, an estimated 299,000 patients will be diagnosed with prostate cancer in 2024.[35] Most cases of prostate cancer—70%—are diagnosed at the local state.[36] A portion of patients' (20%-40%) cancer diagnosed at the local state does recur over time,[37] but the development of metastatic disease remains very low at an estimated 5%.[38] Furthermore, not all patients are treated in the same way. Roughly 42% of cases are diagnosed in patients aged 70 years or older. We consider regional/metastatic disease in this patient population. Separately, in the population that is younger than 70 years old (58%) we consider the population with regional/distant disease as well as those who, upon diagnosis with local disease, experience recurrent metastatic disease. As a result we estimate the market for androgen receptor inhibitory therapy is approximately 95,000 patients.

Nearly all patients receiving frontline androgen receptor therapy will fail and develop castration-resistant prostate cancer. Kairos intends to develop ENV105 for this patient population. The goal is resensetize this patient population to hormonal therapy.

As for pricing, enzalutamide is priced at approximately $15,000 per month. Certain other estimates, however, noted that the insurance annual cost of enzalutamide is approximately $70,000. At this time, we estimate that a hormone therapy-sensitizing drug such as ENV105, if approved, could be price at approximately ~9,000 per month. As a resutl we estimate the annual cost of ENV105 to be approximately $110,000. Note, given the median progression-free survival observed with second-generation androgen receptor inhibitor therapies, it is possible that the duration of treatment with ENV105 maybe significantly longer than 12 months.

We at this time estimate, with 12 months of therapy at $9,000 per month, a peak market adoption of approximately 30%-35%, a late-2028/early-2029 launch, and peak sales occurring in 2033-34, peak revenue with ENV105 in castration-resistant prostate cancer could reach approximately $5.5B. A registration-enabling trialwill need to show a sirvival benefit. We assign a 50% probability of success for ENV105 in this indication.

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[38] Hamdy FC, Donovan JL, Lane JA*, et al.* Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*. 2023;388(17):1547-1558. doi:10.1056/NEJMoa2214122

EGFR-mut NSCLC

Of roughly 230,000 diagnosed lung cancer cases, ~85%-90% of patients present with non-small cell lung cancer cases. Approximately 73% of patients have locally-advanced or metastatic disease.[39] But EGFR mutation occurs a subset (12%) of NSCLC patients.[40] Among adenocarcinoma, ~15% of patients will have EGFR-mutated lung cancer.[41] Osimertinib in combination with chemotherapy has been approved for the treatment of EGFRm NSCLC in the frontline (the FLAURA-2 trial).[42] The majority of patients (an estimated 90%) eventually progress to second line after osimertinib failure.[40] Thus, we estimate that ~16,000 patients in the second line will constitute the market for ENV105 to be used with osimertinib. We estimate a monthly cost of ~$9,000 per month (on par with EVN105 pricng in castration-resistant prostate cancer), approximately 6 months of treatment, a late-2029/early-2030 launch, and peak market adoption of approximately 80% during 2034-35, resulting in ~$1.1B peak sales. We assign a 45% probability of success for ENV105 in this indication.

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ENV201

T-Cell Therapy for Glioblastoma Multiforme (GBM)

Dr. John Yu and colleagues at Cedar-Sinai postulated that active immunotherapy using dendritic cell (DC)-based vaccination to initiate T-cell-mediated antitumor immunity could overcome limitations of conventional treatments for GBM. Recall GBM is the most common and most aggressive type of primary brain tumor occurring in 52% of all primary brain tumor cases. Current treatment of GBM is palliative and includes surgery, radiotherapy and chemotherapy.[43,44] Despite optimal therapy, the prognosis remains poor with median overall survival (OS) of approximately 14-18 months.[45,46]

DCs loaded with tumor antigens can be administrated subcutaneously into patients. The goal is to generate ex vivo a population of antigen-loaded DCs that stimulates robust and long-lasting CD4+ and CD8+ T-cell responses in the patient with cancer. Recent studies identifying cancer stem-like cells (CSCs) as brain tumor-initiating cells may have implications for modifying GBM treatments, including DC vaccination-based immunotherapy.[47,48,49,50] Therapies targeting CSCs may prevent tumor relapse. Some proteins expressed by CSCs are normally seen only in early development stages. CSCs have been found to prolong survival of tumor-bearing animals.[51] But questions remain regarding mechanisms underlying the apparent superior outcomes from CSC-targeting DC vaccination. For example, is there any difference between CSC antigens and conventional tumor lysates in promoting DC maturation and polarization, or in effector cell differentiation and memory T-cell generation *in vivo*? Although higher expression of TAAs in CSCs, as shown in the Gentao study, may be one factor contributing to the outcomes, it is likely other factors in addition to TAA expression levels also play a role.[45]

Wen and colleagues tested ICT-107, an autologous DC immunotherapy in newly diagnosed GBM patients.[52] ICT-107 targets six antigens on both tumor and cancer stem cells and includes the HLA-A1-restricted, melanoma-associated antigen-1 (MAGE-1), an antigen isolated from immunoselected melanoma-2 (AIM-2), the HLA-A2–restricted, human EGFR-2 (HER2/neu) antigen, tyrosinase-related protein-2 TRP-2, glycoprotein 100 (gp100), and IL13 receptor α2 (IL13Rα2). These were selected on the basis of studies that included an analysis of 46 primary GBM tumors.[46,53] Three or more of the selected antigens were expressed on all of the tumors, four or more antigens on 97% of tumors, and five or more antigens on 93% of tumors. All six antigens were expressed on 83% of tumors.

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[51] Xu Q, Liu G, Yuan X, *et al.* Antigen-specific T-cell response from dendritic cell vaccination using cancer stem-like cell-associated antigens. *Stem Cells*. 2009;27(8):1734-1740. doi:10.1002/stem.102

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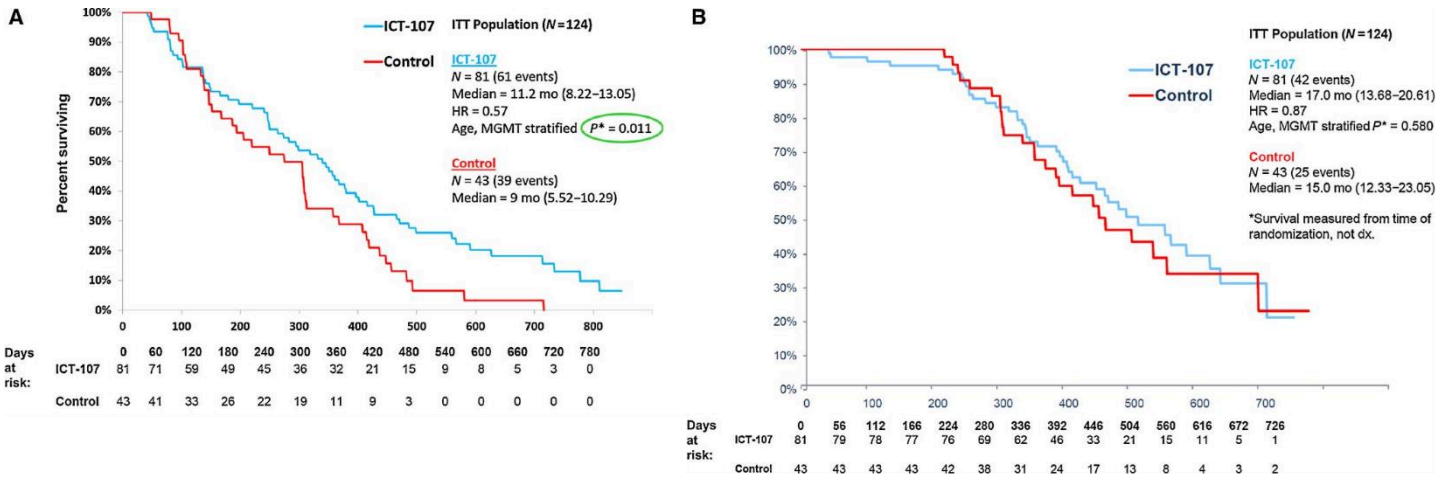
[53] Saikali S, Avril T, Collet B, *et al.* Expression of nine tumour antigens in a series of human glioblastoma multiforme: interest of EGFRvIII, IL-13Ralpha2, gp100 and TRP-2 for immunotherapy. *J Neurooncol*. 2007;81(2):139-148.

A total of 124 patients were randomized to standard-of-care plus either ICT-107 or placebo. There were 43 control patients and 81 active patients representing a 1:2 randomization. Seventy-five (60.5%) were men. The median age was 59.2 (range, 22.9–81.8); median KPS was 90. ICT-107 or placebo and adjuvant temozolomide was administered beginning 1 week after completion of radio-chemotherapy. Patients were stratified by study site and age (<50 years, >50 years). Vaccinations were administered in the armpit on day 21 of cycles 1,3,6 and 10 and every 6 months until study completion or progressive disease.

Figure 16 depicts progression free survival (PFS) and overall survival (OS) of the therapy. The OS for the ICT-107 group in the ITT population was 17 months and was not significantly better than the 15 months (CI: 12.33-23.05) for the control group (HR=0.87; p=0.58). However, the PFS was 11.2 months in the ICT-107 cohort which was statistically significantly increased compared with 9 months for the control group (HR=0.57; p=0.011). The median OS had not been reached by the data cut-off. At 99 events, median OS favored ICT-107 by 1.6 months (HR=0.85; p=0.44 two-sided). PFS, for ICT-107 of 11.4 months was statistically significantly increased over 10.1 months for the control group (HR=0.64; p=0.033).[46]

Figure 16. Overall Survival and Progression Free Survival in GBM Patients Receiving ICT-107



A.PFS, B. OS

Source: Wen PY et al. Clin Cancer Res. 2019;25(19):5799-5807

The authors tested for immune response using interferon γ ELISpot in the ITT population. For responders treated with ICT-107 there was an increase in interferon compared to the control (P = 0.058). These responders had improved overall survival compared with non-responders.[46]

While ICT-107 has been the only immune therapy to generate patient progression free survival it still falls short of improving survival. In order to expand on the Wen *et al.* result, Kairos will generate T-cells from outside the immunosuppressive area in and around the tumor. Those T-cells will be activated, expanded and reinfused back into the brain through an Ommaya reservoir (a plastic reservoir under the scalp that can receive cell infusions. The catheter goes into the ventricle from the subcutaneous reservoir).

Regarding KROS201, the therapeutic consists of autologous activated T-cells that were stimulated by dendritic cells bearing the same antigens from the dendritic cell vaccine that was described in Wen *et al*. above. The activated T-cells in KROS 201 are further stimulated with 3 additional CTL antigens and 9 helper epitopes. The helper epitopes were added to provide T helper cells to the immune response.

An IND for KROS 201 has been submitted and approved by the FDA. We assume a trial will begin in 2025, but this may be capital dependent.

Kairos Pharma: Origination

Kairos Pharma was originally incorporated on June 17, 2013, in the state of California as NanoGB13, Inc. The company changed its name to Kairos Pharma on July 15, 2016. On May 10, 2023, Kairos filed a certificate of conversion with the Secretary of State of the State of California, and on the same date, also filed with the Delaware Secretary of State a certificate of conversion converting the company from a non-Delaware corporation to a Delaware corporation pursuant to section 265 of the Delaware General Corporation Law. In addition, on May 10, 2023, KAPA filed a certificate of incorporation with the State of Delaware, thus completing conversion into a Delaware corporation. In conjunction with the company's conversion into a Delaware corporation, on May 10, 2023, the company conducted a 1-for-2.5 Reverse Stock Split. After the Reverse Stock Split, there were 10,334,357 shares of our common stock outstanding. On November 13, 2019, Kairos entered into a merger agreement with AcTcell Biopharma and issued 5,045,000 shares of its common stock for all the outstanding shares of AcTcell common stock. AcTcell was a California corporation that was incorporated on July 22, 2019. AcTcell's only asset at the merger date was an Exclusive License Agreement dated August 30, 2019, between AcTcell and Cedars-Sinai Medical Center. AcTcell had no liabilities at the merger date. John Yu, the company's Chairman, Chief Executive Officer and majority shareholder, was the sole owner of AcTcell. The acquisition of AcTcell by Kairos was treated as a transaction between entities under common control resulting in the historical costs basis of AcTcell's assets and liabilities being recognized. Enviro Therapeutics or Enviro was incorporated on November 15, 2019, under the law of the state of California and is an early-stage company that is focused on the development of therapeutics targeting the tumor microenvironment to complement conventional and targeted therapies designed against the cancer cells. Kairos's Chairman, Chief Executive Officer and majority shareholder, Dr. Yu, was also a founder and shareholder of Enviro. On June 3, 2021, Kairos and Enviro entered into a share exchange with Kairos acquiring all of the common stock of Enviro in exchange for stock in Kairos. In the Enviro-Kairos share exchange, the Enviro shareholders exchanged 100% of the issued and outstanding shares of Enviro (on a fully diluted basis) for 6,000,000 shares of newly issued restricted common stock of Kairos, which, as of the closing of the Enviro-Kairos share exchange: (i) represented approximately twenty percent (20%) of the outstanding shares of capital stock of the company on a fully diluted basis (ii) have voting power approximately equal to twenty percent (20%) of all shares eligible to vote on matters by the shareholders of Kairos. At the closing of the Enviro-Kairos share exchange, Kairos issued each of Dr. Yu and Dr. Neil Bhowmick (the other co-founder of Enviro) 1,860,000 of Kairos' restricted common stock in exchange for their shares of Enviro. Kairos also issued Tracon Pharmaceutical, an unaffiliated third party, 280,000 shares of Kairos' restricted common stock in exchange from their shares of Enviro, which Tracon had received pursuant to a license and supply agreement between Enviro and Tracon. Prior to the 1-for-2.5 reverse split conducted in 2023 and including the newly issued shares in that transaction, Kairos had approximately 19,825,957 shares of common stock issued and outstanding on a fully diluted basis (including 18,825,957 outstanding shares of common stock, and 1,000,000 warrants exercisable into 1,000,000 shares of common stock).

Intellectual Property

Dr. Yu, Dr. Bhowmick, and Dr. Murali have developed certain proprietary technology, and identified other proprietary technology developed by researchers at Cedars-Sinai. Proprietary technology invented and developed by doctors and scientists and Cedars-Sinai is owned by Cedars-Sinai. However, that technology is or can be licensed to 3rd parties in partnership with Cedars-Sinai. Kairos and the subsidiary Enviro have multiple such options and/or license agreements with Cedars-Sinai regarding proprietary technology.

Kairos Intellectual Property Agreements with Cedars-Sinai Medical Center

Kairos has entered into four Exclusive License Agreements with Cedars-Sinai Medical Center, which grant Kairos exclusive licensing rights (including the right to sublicense) with respect to certain patent rights owned by Cedars-Sinai: (1) Method of generating activated T-cells for cancer therapy, invented by Dr. John S. Yu and others; (2) Methods of use of compounds that bind to RelA of NFkB, invented by Dr. Ramanchandran Murali and others; (3) Composition and methods for treating fibrosis, invented by Dr. Ramanchandran Murali and others; and (4) Compositions and methods for treating cancer and autoimmune diseases, invented by Dr. Ramanchandran Murali and others. For the exclusive license agreement in item 1 above, Kairos is required to pay royalties based on low single-digit percentage of patent product sales and less than one percent of other sales as well as other non-royalty sublicense fees ranging from a mid-single-digit to low double-digit percentage of such revenues shall be due and payable to Cedars, depending on the stage of FDA authorization at the time the sublicense revenue is generated. Non-royalty sublicense revenue would be between 5% and 35% depending on the phase of FDA testing of the product depending on when the sublicense agreement is signed. In addition, Kairos is required to pay Cedars based on the following milestones: (i) successfully completing Phase 1 clinical trial; (ii) successfully completing a Phase 2 clinical trial and receipt of FDA or equivalent regulatory agency in another jurisdiction approval for a Phase 3 clinical trial; (iii) receipt of FDA approval; and (iv) cumulative net sales exceeding $50,000,000. If all of these milestones are met, the required milestone payments will total $4.4M. For each of the exclusive license agreement in items 2, 3 and 4, Kairos is required to pay royalties based on a low single-digit percentage of net sales.

Patent expiration dates and specific jurisdictions of foreign patents in-licensed from Cedars-Sinai are listed below (Figure 17).

Enviro Intellectual Property Agreements with Cedars-Sinai Medical Center

On March 16, 2020, Enviro entered into two Exclusive Option Agreements with Cedars-Sinai Medical Center that give Enviro options to enter into an Exclusive Agreement with Cedars which would grant Enviro exclusive licensing rights (which include the right to sublicense) to certain patent rights owned by Cedars.

In consideration of these agreements, Enviro agreed to pay option fees of $2,000 and $3,000, respectively. Enviro's options expire nine months from the effective date. On January 9, 2021, and January 11, 2021, the parties agreed to extend both nine-month option periods for an additional six months. In consideration of these extensions, Enviro agreed to pay an extension fee of $500, and $1,000, respectively. Enviro entered into two Exclusive License Agreements with Cedars-Sinai Medical Center on June 2, 2021. Enviro and Cedars entered into: (1) an Exclusive License Agreement for Enviro to develop, manufacture, use and sell products utilized or derived from patent rights worldwide, which include one patent application in the United States related to the "Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial DNA from Circulation and for Detection of Mitochondrial DNA" invented by Dr. Neil Bhowmick and others; and (2) an Exclusive License Agreement for Enviro to develop, manufacture, use and sell products derived from the patent rights and technical information worldwide, which include six patent applications in the United States, Australia, Canada, China, Europe and Japan related to the "Sensitization of Tumors to Therapies Through Endoglin Antagonism" invented by Dr. Neil Bhowmick and others. The milestones agreed to were as follows: 1. Completion of preclinical studies within two years of the effective date, 2. Completion of toxicology studies within two and a half years of the Effective Date; 3. Obtaining IND within three years of the Effective Date; and 4. Beginning Phase 1 trial within four years of the Effective Date. Milestones 1,3 and 3 have completed. As of September 2023, Kairos completed milestones 1, 2 and

3. The aggregate potential fees that Enviro may have to pay in exchange for the licenses is approximately $690,000 as of August 16, 2024. Together, Kairos and Enviro owe a total of approximately $950,000 to Cedars, of which $750,000 will be converted into 312,500 shares of common stock. Cedars shall also receive royalty payments of a mid-single-digit percentage of net sales of products associated with the licensed patent right and less than one percent of net sales of other products derived from Cedars' technical information, with a minimum royalty year in the low five-digits due beginning on the third anniversary of the effective date of the license. Non-royalty sublicense revenue would be between 5% and 35% depending on the phase of FDA testing of the product during which the sublicense agreement is signed. Enviro shall pay Cedars in connection with achieving certain milestones relating to products derived from the patent rights: (i) successful completion of Phase 1 clinical trial; (ii) successful completion of Phase 2 clinical trial, receipt of FDA approval, and approval for a Phase 3 clinical trial; (iii) FDA approval of a new drug application or biologics license applications; and (iv) cumulative net sales exceeding $100,000,000. The maximum aggregate milestone payment for ENV 105 will be $7,150,000 when cumulative net sales have exceeded $100,000,000. The last-to-expire of licensed patents is scheduled to expire on June 14, 2037.

Enviro License and Supply Agreement with Tracon Pharmaceuticals

On May 21, 2021, Enviro entered into an Enviro-Tracon license agreement with Tracon. Pursuant to the Enviro-Tracon license agreement, Tracon grants to Enviro access to inactive IND filings for "TRC105" in the United States, ownership of "TRC105" stored vials of drug product manufactured to GMP standards stored at Fisher Clinical or their designee, and assignment of Tracon's patent rights to its "CD105 technologies." Dr. Bhowmick, our Chief Scientific and Enviro's CEO, is a consultant at Tracon Pharmaceuticals.

Pursuant to the Enviro-Tracon license agreement, Enviro paid Tracon an upfront fee of $100,000, and is obligated to pay Tracon an additional $500,000 upon its completion of one or more financings through the sale of equity in an amount of $10,000,000, and an additional $500,000 within 10 days of its completion of one or more financings through the sale of equity (or debt convertible to equity) in an amount of $22,000,000. In addition, Enviro is obligated to pay Tracon a royalty of 3% of net sales on a country-by-country basis of the products subject to the agreement, and non-royalty payments of 3% of consideration for sublicensing fees. Enviro issued Tracon equity ownership in Enviro equal to a number of shares of restricted common stock of Enviro equal to 7% on a fully diluted and converted basis of all common and preferred shares of Enviro. In connection with the Enviro-Kairos share exchange, the parties agreed that Tracon would receive, in exchange for its Enviro common stock, 280,000 shares of the restricted common stock of Kairos (which is equal to 1.41229% of the issued and outstanding shares of Kairos on a fully diluted basis). Pursuant to the Enviro-Tracon license agreement, we have exclusive licensing rights (which include the right to sublicense) to eight issued U.S. patents, four U.S. utility or provisional patent applications, 24 issued patents and 24 patent applications in foreign jurisdictions.

Figure 17. Patents Patent Type, Jurisdiction and Expiration

Name of the Patent	Patent/Application No.	Status	Related Products/Technology	Type of Patent Protection	Expiration	Jurisdiction
Endoglin Antibodies	8,221,753	Granted	ENV 105	Product	3/31/2030	USA
Endoglin Antibodies	9,150,652	Application	ENV 105	Method of treatment	9/30/2029	USA
Endoglin Antibodies	9,944,714	Granted	ENV 105	Composition of matter	3/31/2030	USA
Antibody Formulations and Uses Thereof	201810659773.9	Application	ENV 105	Product and Method of Treatment	9/5/2033	China
Antibody Formulations and Uses Thereof	1538/DELNP/2015	Application	ENV 105	Product and Method of Treatment	9/5/2033	India
Antibody Formulations and Uses Thereof	6445671	Granted	ENV 105	Product and Method of Treatment	9/5/2033	Japan
Antibody Formulations and Uses Thereof	6602446	Granted	ENV 105	Product and Method of Treatment	9/5/2033	Japan
Antibody Formulations and Uses Thereof	368996	Granted	ENV 105	Product and Method of Treatment	9/5/2033	Mexico
Antibody Formulations and Uses Thereof	10,195,281	Granted	ENV 105	Product and Formulation	12/25/2034	USA
Antibody Formulations and Uses Thereof	1501001224	Application	ENV 105	Product and Method of Treatment	9/5/2033	Thailand
Antibody Formulations and Uses Thereof	MY-180157-A	Granted	ENV 105	Product and Method of Treatment	9/5/2033	Malaysia
Methods and Use of Compounds that Bind to RelA of NF-kB	16804352.9	Application	KROS 301	Product and Method of Treatment	6/1/2036	Europe
Methods and Use of Compounds that Bind to RelA of NF-kB	10,881,641	Granted	KROS 301	Method of treatment	11/30/2037	USA
Compositions and Methods for Treating Fibrosis	3194446	Granted	KROS 401	Product and Method of Treatment	9/18/2035	Europe
Compositions and Methods for Treating Fibrosis	7095990	Granted	KROS 401	Product and Method of Treatment	9/18/2035	Japan
Compositions and Methods for Treating Fibrosis	10,245,298	Granted	KROS 401	Pharmaceutical composition	9/18/2035	USA
Compositions and Methods for Treating Fibrosis	11,547,738	Granted	KROS 401	Method of treatment	9/18/2035	USA
Compositions and Methods for Treating Fibrosis	18/093,667	Application	KROS 401	Product and Method of Treatment	9/18/2035	USA
Compositions and Methods for Treating Cancer and Autoimmune Diseases	3,108,796	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	Canada
Compositions and Methods for Treating Cancer and Autoimmune Diseases	201980062092.7	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	China
Compositions and Methods for Treating Cancer and Autoimmune Diseases	19848154.1	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	Europe
Compositions and Methods for Treating Cancer and Autoimmune Diseases	2021-506687	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	Japan
Compositions and Methods for Treating Cancer and Autoimmune Diseases	10-2021-7006602	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	South Korea
Compositions and Methods for Treating Cancer and Autoimmune Diseases	17/266,488	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	USA
Method of Generating Activated T Cells for Cancer Therapy	3,150,273	Application	KROS 201	Product and Method of Treatment	8/10/2040	Canada
Method of Generating Activated T Cells for Cancer Therapy	20850517.2	Application	KROS 201	Product and Method of Treatment	8/10/2040	Europe
Method of Generating Activated T Cells for Cancer Therapy	17/633,505	Application	KROS 201	Product and Method of Treatment	8/10/2040	USA
Sensitization of Tumors to Therapies Through Endoglin Antagonism	2017286561	Application	ENV 105	Product and Method of Treatment	6/14/2037	Australia
Sensitization of Tumors to Therapies Through Endoglin Antagonism	3026066	Application	ENV 105	Product and Method of Treatment	6/14/2037	Canada
Sensitization of Tumors to Therapies Through Endoglin Antagonism	201780050000.4	Application	ENV 105	Product and Method of Treatment	6/14/2037	China
Sensitization of Tumors to Therapies Through Endoglin Antagonism	17814046.3	Application	ENV 105	Product and Method of Treatment	6/14/2037	Europe
Sensitization of Tumors to Therapies Through Endoglin Antagonism	7092684	Granted	ENV 105	Product and Method of Treatment	6/14/2037	Japan
Sensitization of Tumors to Therapies Through Endoglin Antagonism	17/685,040	Application	ENV 105	Product and Method of Treatment	6/14/2037	USA
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	3162518	Application	ENV 205	Product and Method of Treatment	11/25/2040	Canada
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	20893032.1	Application	ENV 205	Product and Method of Treatment	11/25/2040	Europe
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	2022-530781	Application	ENV 205	Product and Method of Treatment	11/25/2040	Japan
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	17/779,716	Application	ENV 205	Product and Method of Treatment	11/25/2040	USA
Compositions and Methods for Treating Cancer and Autoimmune Diseases	19848154.1	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	Europe
Compositions and Methods for Treating Cancer and Autoimmune Diseases	2021-506687	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	Japan
Compositions and Methods for Treating Cancer and Autoimmune Diseases	10-2021-7006602	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	South Korea
Compositions and Methods for Treating Cancer and Autoimmune Diseases	17/266,488	Application	KROS 101 and KROS 102	Product and Method of Treatment	8/8/2039	USA
Method of Generating Activated T Cells for Cancer Therapy	3,150,273	Application	KROS 201	Product and Method of Treatment	8/10/2040	Canada
Method of Generating Activated T Cells for Cancer Therapy	20850517.2	Application	KROS 201	Product and Method of Treatment	8/10/2040	Europe
Method of Generating Activated T Cells for Cancer Therapy	17/633,505	Application	KROS 201	Product and Method of Treatment	8/10/2040	USA
Sensitization of Tumors to Therapies Through Endoglin Antagonism	2017286561	Application	ENV 105	Product and Method of Treatment	6/14/2037	Australia
Sensitization of Tumors to Therapies Through Endoglin Antagonism	3026066	Application	ENV 105	Product and Method of Treatment	6/14/2037	Canada
Sensitization of Tumors to Therapies Through Endoglin Antagonism	201780050000.4	Application	ENV 105	Product and Method of Treatment	6/14/2037	China
Sensitization of Tumors to Therapies Through Endoglin Antagonism	17814046.3	Application	ENV 105	Product and Method of Treatment	6/14/2037	Europe
Sensitization of Tumors to Therapies Through Endoglin Antagonism	7092684	Granted	ENV 105	Product and Method of Treatment	6/14/2037	Japan
Sensitization of Tumors to Therapies Through Endoglin Antagonism	17/685,040	Application	ENV 105	Product and Method of Treatment	6/14/2037	USA
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	3162518	Application	ENV 205	Product and Method of Treatment	11/25/2040	Canada
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	20893032.1	Application	ENV 205	Product and Method of Treatment	11/25/2040	Europe
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	2022-530781	Application	ENV 205	Product and Method of Treatment	11/25/2040	Japan
Compositions and Methods for Treating Diseases and Conditions by Depletion of Mitochondrial or Genomic DNA From Circulation	17/779,716	Application	ENV 205	Product and Method of Treatment	11/25/2040	USA

Source: Kairos S-1, 2024

Manufacturing

At this time,. Kairos does not seek to build a manufacturing facility. Rather, it will rely on external vendors that are compliant with current “Good Manufacturing Practices”.

Competition

With respect to KROS-101, it faces potential competition from several GITR focused monoclonal antibody products that are currently under development, including multiple candidates from large pharmaceutical companies, all of which are either Phase 1 or Phase 2 clinical trial.

In targeted immunotherapy, Kairos’ KROS-102 candidate would compete with several monoclonal antibody-based products that target PD-1 or PD-L1 proteins. Such PD-1 or PD-L1 inhibitors activate the immune system to attack tumors and are used to treat certain types of cancer. KROS-101 is a small molecule, which is anticipated to be significantly less expensive to manufacture than a monoclonal antibody-based product. In the area of cell therapy only two products produced by large pharmaceutical companies have been approved for marketing in the United States. However, Kairos estimates that more than 150 clinical trials are currently in progress.

Kairos believes the competitive factors that will affect the development and commercial success of the lead product candidate, ENV105. If successful there are or will likely be other agents that in the future may address resistance mechanisms of therapeutics used for prostate cancer.

Compounds such as Pluvicto, the experimental masked T-cell engager JANX007 from Janux Therapeutics (JANX; Not Rated), an experimental masked T-cell engager VIR-5500 from Vir Biotechnology (VIR; Not Rated), and others would be utilized after androgen signaling therapy.

Pluvicto is a radioligand therapeutic agent indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic CRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

JANX007 and VIR-5500 are CD3-binding T-cell engagers that target PSMA.

A possible competitor to ENV105 is an oral androgen receptor ligand-directed degrader and antagonist from Bristol Myers Squibb (BMY; Not Rated) known as BMS-986365. Rathkoft *et al.* discussed the safety and clinical activity of BMS-986365 in a recent paper.[54] BMS-986365 targets the androgen receptor via a first-in-class dual mechanism of AR degradation and antagonism. Data from a phase 1 multicenter study of BMS-986365 conducted in heavily pretreated patients with progressive mCRPC suggest BMS-986365 was well tolerated, with a manageable safety profile, and demonstrated activity with potentially higher benefit in chemotherapy-naive patients. These data show the potential of BMS-986365 to overcome resistance to current androgen receptor pathway inhibitors, regardless of androgen receptor mutation status.

Financials

In order to complete the Phase 2 trial for prostate cancer for ENV105, Kairos has stated if requires $1.7M. The ENV105 Phase 1 trial for non-small cell lung cancer will be completed with no additional funding as it is fully funded by grants from a donor whose name (individual or foundation) is not known to us. For preclinical development of KROS101, KROS301 and KROS401, Kairos has estimated the requirement of $3.2M.

Kairos stated it intends to advance one drug at a time, depending on the availability of funds. Kairos has $3.2M in cash as of September 30, 2024. The company will need to raise additional capital to advance its lead asset ENV105 in registration-enabling trials in one of more indications.

[54] Rathkopf DE, Patel MR, Choudhury AD, *et al*. Safety and clinical activity of BMS-986365 (CC-94676), a dual androgen receptor ligand-directed degrader and antagonist, in heavily pretreated patients with metastatic castration-resistant prostate cancer. *Ann Oncol*. Published online September 16, 2024. doi:10.1016/j.annonc.2024.09.005

Management

Kairos management, with the exception of CFO Doug Samelson, are part-time employees. All maintain academic appointments at Cedars Sinai in Los Angeles. This is consistent with the foundation of the company's origin. At present this may also lower overall costs. However, progression of clinical trials will necessitate a greater team focus.

John S. Yu, MD
CEO & Chairman

- Professor and Clinical Chief of Neurosurgery, Director of the Brain Tumor Center at Cedars Sinai Medical Center.
- Developed numerous immunotherapies and nanotechnologies from his NIH funded laboratory.
- Developed 8 new investigational drugs with the FDA and has led numerous clinical trials.
- Former officer of ImmunoCellular Therapeutics.
- BAS from Stanford, MD from Harvard Medical School and MIT.
- Immunology Fellowship at the Institut Pasteur, Paris, Neurosurgery Residency at Massachusetts General Hospital/Harvard.

Ramachandran Murali, Ph.D
VP, Research and Development

- Associate Professor, Biomedical Sciences and Research in Immunology at Penn/Cedars Sinai Medical Center.
- Leading expert in X-ray crystallography, biophysical, biochemical, and immunology fields, having made significant advances in molecular engineering and cell surface receptors by developing pharmacological agents which include new paradigms in structure-based peptidomimetics drug discovery.
- Developed numerous technologies that reverse key mechanisms of immune suppression of cancer.

Neil Bhowmick, Ph.D
Chief Scientific Officer

- Professor of the Department of Medicine and Director of the Cancer Biology Program at Cedars-Sinai Medical Center.
- Fellowship at Vanderbilt University Medical Center Research Director, Oppenheimer Urologic Reference Laboratory (OURLab).
- Holds 6 patents for biomarker detection platforms and stromal targeted therapeutics (inclusive of ENV105 and ENV205).
- Consultant at Xencor Inc. (XNCR; Not Rated) and Tracon Pharma (TCON; Not Rated).
- NCI/NIH funded for over 15 years and cited over 11,700 times.

Doug Samuelson
Chief Financial Officer

- Finance & accounting professional with over 25 years of experience.
- Certified Accountant and current CFO of Wellness Center, USA Inc.
- Held numerous former CFO positions including Second Sight Medical Products, Inc., AdvaVet, Inc. and Solis Tek, Inc.
- MSc, Computer Science from California State University, BSc, Accounting from University of Utah.

Rodman & Renshaw, LLC
KAPA | Kairos Pharma
Statement on Operations ($M except for EPS estimates)

Tony Butler, Ph.D.
tbutler@rodm.com

	Q124A	Q224A	Q324A	Q424E	2024E	Q125E	Q225E	Q325E	Q425E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E
Revenue																		
ENV-105 prostate cancer, risk-adj					-						-	-	-	27.8	200.5	495.3	965.7	1,539.3
ENV-105 EGFmut NSCLC, risk-adj											-	-	-	-	2.4	52.3	147.0	267.7
Ex-US royalties, risk-adj					-						-	-	-	-	2.3	18.4	46.5	93.6
Other					-													
Total revenue	-	-	-	-	-	-	-	-	-	-	-	-	-	**27.8**	**205.3**	**566.0**	**1,159.2**	**1,900.6**
Operating and non-operating expenses																		
COGS					-					-				24.0	96.0	240.0	360.0	432.0
Gross revenue			-	-	-	-	-	-	-	-	-	-	-	3.8	109.3	326.0	799.2	1,468.6
Gross margin (excl. royalties)													-	*13.6%*	*52.7%*	*56.2%*	*67.6%*	*76.1%*
Research & development			0.0	0.1	0.2	0.7	3.5	5.3	7.9	17.3	86.6	173.3	259.9	270.3	281.1	292.3	304.0	316.2
General & administrative			0.4	1.1	1.5	2.2	2.3	2.4	2.6	9.5	10.0	11.0	22.0	44.1	45.9	47.7	49.6	51.6
Sales & marketing					-					-		-	50.0	87.5	131.3	136.5	142.0	147.6
Royalty expenses					-					-			-	1.1	8.2	25.5	52.2	95.0
Total operating expenses			0.4	1.2	1.6	2.9	5.8	7.7	10.4	26.9	96.6	184.3	331.9	427.0	562.4	742.0	907.7	1,042.4
Operating income (loss)			**(0.4)**	**(1.2)**	**(1.6)**	**(2.9)**	**(5.8)**	**(7.7)**	**(10.4)**	**(26.9)**	**(96.6)**	**(184.3)**	**(331.9)**	**(423.2)**	**(453.1)**	**(416.0)**	**(108.5)**	**426.2**
Net interest income (expenses)			(0.5)	0.0	(0.5)	0.0	0.1	0.1	0.0	0.2	0.5	0.6	0.9	1.3	0.9	0.8	2.5	0.4
Other income (expenses)			(0.1)		(0.1)					-								
Pre-tax income (loss)			**(1.0)**	**(1.2)**	**(2.3)**	**(2.9)**	**(5.7)**	**(7.6)**	**(10.4)**	**(26.7)**	**(96.1)**	**(183.7)**	**(331.0)**	**(421.9)**	**(452.3)**	**(415.2)**	**(106.0)**	**426.5**
Income taxes (benefit)				-	-	-	-	-	-	-	-	-	-	-	-	-	-	17.9
Tax rate (%)																		
Net income (loss)			**(1.0)**	**(1.2)**	**(2.3)**	**(2.9)**	**(5.7)**	**(7.6)**	**(10.4)**	**(26.7)**	**(96.1)**	**(183.7)**	**(331.0)**	**(421.9)**	**(452.3)**	**(415.2)**	**(106.0)**	**408.6**
EPS																		
Basic EPS, non-GAAP			**(0.08)**	**(0.10)**	**(0.18)**	**(0.14)**	**(0.27)**	**(0.36)**	**(0.36)**	**(1.15)**	**(2.60)**	**(3.31)**	**(4.26)**	**(4.42)**	**(4.11)**	**(3.40)**	**(0.84)**	**3.16**
Diluted EPS, non-GAAP			**(0.08)**	**(0.10)**	**(0.18)**	**(0.14)**	**(0.27)**	**(0.36)**	**(0.36)**	**(1.15)**	**(2.60)**	**(3.31)**	**(4.26)**	**(4.42)**	**(4.11)**	**(3.40)**	**(0.84)**	**3.16**
Basic common shares outstanding			12.8	12.9	12.9	21.0	21.1	21.2	29.2	23.1	37.0	55.6	77.6	95.5	110.1	122.0	125.7	129.4
Diluted common shares outstanding			12.8	12.9	12.9	21.0	21.1	21.2	29.2	23.1	37.0	55.6	77.6	95.5	110.1	122.0	125.7	129.4

Source: Company press releases, SEC filings, Rodman & Renshaw Esimates

Margin analysis																		
COGS (excl. royalties)																43.8%	32.4%	23.9%
R&D																51.6%	26.2%	16.6%
G&A																8.4%	4.3%	2.7%
S&M																24.1%	12.2%	7.8%
Royalty																4.5%	4.5%	5.0%
OPEX																131.1%	78.3%	54.8%
Drivers																		
COGS growth															300%	150%	50%	20%
R&D growth											400%	100%	50%	4%	4%	4%	4%	4%
G&A growth											5%	10%	100%	100%	4%	4%	4%	4%
Sales force headcount													50	100	150			
Sales force expense growth																4%	4%	4%
Marketing expenses growth													100%	50%	50%	4%	4%	4%
Royalty-Cedars-Sinai														4.0%	4.0%	4.5%	4.5%	5.0%
Cash in hand			3.2	2.0		19.1	13.4	5.7	25.3		29.2	45.5	64.5	42.6	40.3	125.1	19.1	427.7

Rodman & Renshaw, LLC
KAPA | Kairos Pharma
Revenue Build

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	POS	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E
ENV-105																		
Prostate cancer after 1L hormone therapy failure																		
US sales ($M)		-	-	-	-	-	62	446	1,101	2,146	3,421	5,218	5,349	5,483	5,621	5,761	5,905	6,052
Risk-adj. sales ($M; 10% G2N)	50%	-	-	-	-	-	28	201	495	966	1,539	2,348	2,407	2,468	2,529	2,593	2,657	2,724
Europe sales ($M)		-	-	-	-	-	-	39	303	705	1,373	2,160	3,419	3,472	3,525	3,580	3,635	3,691
Europe royalty	12%	-	-	-	-	-	-	5	36	85	165	259	410	417	423	430	436	443
Risk-adj Europe royalty	50%			-	-	-	-	2	18	42	82	130	205	208	212	215	218	221
EGFRmut NSCLC 2L osimertinib combo																		
US sales ($M)		-	-	-	-	-	-	5	116	327	595	864	1,049	1,075	1,102	1,129	1,158	1,187
Risk-adj. sales ($M)	45%	-	-	-	-	-	-	2	52	147	268	389	472	484	496	508	521	534
Europe sales ($M)		-	-	-	-	-	-	-	4	78	208	385	534	673	683	694	704	715
Europe royalty	12%	-	-	-	-	-	-	-	0	9	25	46	64	81	82	83	85	86
Risk-adj Europe royalty	45%	-	-	-	-	-	-	-	0	4	11	21	29	36	37	37	38	39

Source: Rodman & Renshaw Esimates

Rodman & Renshaw, LLC
KAPA | Kairos Pharma
ENV-105 Prostate Cancer Model

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	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E
U.S. Market																	
Population (millions)	345	347	350	352	354	356	358	360	362	364	366	368	369	371	373	375	377
% growth	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Addressable population																	
New cases of Prostate Cancer	299,000	300,776	302,545	304,306	306,060	307,806	309,545	311,276	313,000	314,715	316,423	318,123	319,815	321,499	323,174	324,842	326,502
% incidence	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%	0.09%
>70 years old population	125,580	126,326	127,069	127,809	128,545	129,279	130,009	130,736	131,460	132,180	132,898	133,612	134,322	135,029	135,733	136,434	137,131
% of all prostate cancer	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%
Regional/metastatic disease	**37,674**	**37,898**	**38,121**	**38,343**	**38,564**	**38,784**	**39,003**	**39,221**	**39,438**	**39,654**	**39,869**	**40,083**	**40,297**	**40,509**	**40,720**	**40,930**	**41,139**
% of all prostate cancer	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
<70 years old population	173,420	174,450	175,476	176,498	177,515	178,528	179,536	180,540	181,540	182,535	183,525	184,511	185,493	186,469	187,441	188,408	189,371
% of all prostate cancer	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%
Regional/metastatic disease	**52,026**	**52,335**	**52,643**	**52,949**	**53,254**	**53,558**	**53,861**	**54,162**	**54,462**	**54,760**	**55,058**	**55,353**	**55,648**	**55,941**	**56,232**	**56,523**	**56,811**
% of all prostate cancer	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
Localized disease	121,394	122,115	122,833	123,548	124,260	124,969	125,675	126,378	127,078	127,774	128,468	129,158	129,845	130,528	131,209	131,886	132,560
% of all prostate cancer	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
Disease recurrence/progression w/ mets	**6,070**	**6,106**	**6,142**	**6,177**	**6,213**	**6,248**	**6,284**	**6,319**	**6,354**	**6,389**	**6,423**	**6,458**	**6,492**	**6,526**	**6,560**	**6,594**	**6,628**
% of all prostate cancer	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Eligible patients	**95,770**	**96,339**	**96,905**	**97,469**	**98,031**	**98,590**	**99,147**	**99,702**	**100,254**	**100,803**	**101,350**	**101,895**	**102,437**	**102,976**	**103,513**	**104,047**	**104,578**
Market penetration																	
Patients treated	-	-	-	-	-	493	3,455	8,286	15,686	24,275	35,948	35,780	35,610	35,440	35,268	35,096	34,922
% penetration	0%	0%	0%	0%	0%	1%	3%	8%	16%	24%	35%	35%	35%	34%	34%	34%	33%
Cost per month	9,000	9,270	9,548	9,835	10,130	10,433	10,746	11,069	11,401	11,743	12,095	12,458	12,832	13,217	13,613	14,022	14,442
% growth	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
Months of treatment	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Avg. cost of therapy ($)	108,000	111,240	114,577	118,015	121,555	125,202	128,958	132,826	136,811	140,916	145,143	149,497	153,982	158,602	163,360	168,260	173,308
Patients on therapy	-	-	-	-	-	493	3,455	8,286	15,686	24,275	35,948	35,780	35,610	35,440	35,268	35,096	34,922
Sales ($M)	-	-	-	-	-	62	446	1,101	2,146	3,421	5,218	5,349	5,483	5,621	5,761	5,905	6,052

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Europe Market																	
Population (millions)	745	745	746	746	747	747	747	748	748	749	749	749	750	750	751	751	751
% growth	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
Addressable population																	
New cases of Prostate Cancer	473,579	473,860	474,139	474,415	474,688	474,959	475,227	475,493	475,756	476,017	476,275	476,531	476,785	477,036	477,284	477,531	477,775
% incidence	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%
>70 years old population	198,903	199,021	199,138	199,254	199,369	199,483	199,595	199,707	199,818	199,927	200,036	200,143	200,250	200,355	200,459	200,563	200,665
% of all prostate cancer	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%	42%
Regional/metastatic disease	**59,671**	**59,706**	**59,741**	**59,776**	**59,811**	**59,845**	**59,879**	**59,912**	**59,945**	**59,978**	**60,011**	**60,043**	**60,075**	**60,107**	**60,138**	**60,169**	**60,200**
% of all prostate cancer	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
<70 years old population	274,676	274,839	275,000	275,161	275,319	275,476	275,632	275,786	275,939	276,090	276,240	276,388	276,535	276,681	276,825	276,968	277,109
% of all prostate cancer	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%	58%
Regional/metastatic disease	**82,403**	**82,452**	**82,500**	**82,548**	**82,596**	**82,643**	**82,690**	**82,736**	**82,782**	**82,827**	**82,872**	**82,916**	**82,961**	**83,004**	**83,047**	**83,090**	**83,133**
% of all prostate cancer	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
Localized disease	192,273	192,387	192,500	192,612	192,723	192,833	192,942	193,050	193,157	193,263	193,368	193,472	193,575	193,677	193,777	193,877	193,977
% of all prostate cancer	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
Disease recurrence/progression w/ mets	**9,614**	**9,619**	**9,625**	**9,631**	**9,636**	**9,642**	**9,647**	**9,653**	**9,658**	**9,663**	**9,668**	**9,674**	**9,679**	**9,684**	**9,689**	**9,694**	**9,699**
% of all prostate cancer	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Eligible patients	**151,687**	**151,777**	**151,867**	**151,955**	**152,043**	**152,129**	**152,215**	**152,300**	**152,385**	**152,468**	**152,551**	**152,633**	**152,714**	**152,795**	**152,874**	**152,953**	**153,031**
Market penetration																	
Patients treated	-	-	-	-	-	-	457	3,494	7,962	15,192	23,441	36,372	36,209	36,047	35,885	35,724	35,564
% penetration	0%	0%	0%	0%	0%	0%	0%	2%	5%	10%	15%	24%	24%	24%	23%	23%	23%
Cost per month	6,300	6,426	6,555	6,686	6,819	6,956	7,095	7,237	7,381	7,529	7,680	7,833	7,990	8,150	8,313	8,479	8,649
% growth	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Months of treatment	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Avg. cost of therapy ($)	75,600	77,112	78,654	80,227	81,832	83,469	85,138	86,841	88,577	90,349	92,156	93,999	95,879	97,797	99,753	101,748	103,783
Patients on therapy	-	-	-	-	-	-	457	3,494	7,962	15,192	23,441	36,372	36,209	36,047	35,885	35,724	35,564
Sales ($M)	-	-	-	-	-	-	39	303	705	1,373	2,160	3,419	3,472	3,525	3,580	3,635	3,691

Source: Rodman & Renshaw Esimates

Rodman & Renshaw, LLC
KAPA | Kairos Pharma
ENV-105 EGFR NSCLC Model

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	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E
U.S. Market																	
Population (millions)	345	347	350	352	354	356	358	360	362	364	366	368	369	371	373	375	377
% growth	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Addressable population																	
New cases of Lung cancer	234,580	235,973	237,361	238,743	240,119	241,489	242,853	244,211	245,563	246,909	248,249	249,583	250,910	252,231	253,546	254,854	256,156
% incidence	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%
Metastatic NSCLC (grade 3/4)	148,982	149,867	150,748	151,626	152,500	153,370	154,236	155,099	155,957	156,812	157,663	158,510	159,353	160,192	161,027	161,858	162,685
% of all lung cancer is NSCLC	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%
% NSCLC are metastatic	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%
EGFRmut mNSCLC	17,878	17,984	18,090	18,195	18,300	18,404	18,508	18,612	18,715	18,817	18,920	19,021	19,122	19,223	19,323	19,423	19,522
% mNSCLC are EGFRmut	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%
2L Pts. after Osimertinib in 1L	**16,090**	**16,186**	**16,281**	**16,376**	**16,470**	**16,564**	**16,657**	**16,751**	**16,843**	**16,936**	**17,028**	**17,119**	**17,210**	**17,301**	**17,391**	**17,481**	**17,570**
% of 1L	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%
Market penetration																	
Patients treated	-	-	-	-	-	-	83	1,750	4,777	8,443	11,904	14,029	13,962	13,895	13,828	13,760	13,692
% penetration	0%	0%	0%	0%	0%	0%	1%	10%	28%	50%	70%	82%	81%	80%	80%	79%	78%
Cost per month	9,000	9,270	9,548	9,835	10,130	10,433	10,746	11,069	11,401	11,743	12,095	12,458	12,832	13,217	13,613	14,022	14,442
% growth	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
Months of treatment	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Avg. cost of therapy ($)	54,000	55,620	57,289	59,007	60,777	62,601	64,479	66,413	68,406	70,458	72,571	74,749	76,991	79,301	81,680	84,130	86,654
Patients on therapy	-	-	-	-	-	-	83	1,750	4,777	8,443	11,904	14,029	13,962	13,895	13,828	13,760	13,692
Sales ($M)	-	-	-	-	-	-	5	116	327	595	864	1,049	1,075	1,102	1,129	1,158	1,187

Europe Market																	
Population (millions)	745	745	746	746	747	747	747	748	748	749	749	749	750	750	751	751	751
% growth	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.06%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
Addressable population																	
New cases of Lung cancer	484,887	485,175	485,461	485,743	486,023	486,301	486,575	486,847	487,117	487,384	487,648	487,910	488,170	488,427	488,681	488,934	489,183
% incidence	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%	0.07%
Metastatic NSCLC (grade 3/4)	307,952	308,135	308,316	308,496	308,673	308,850	309,024	309,197	309,368	309,538	309,706	309,872	310,037	310,200	310,362	310,522	310,680
% of all lung cancer	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%	87%
% NSCLC	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%	73%
EGFRmut mNSCLC	36,954	36,976	36,998	37,019	37,041	37,062	37,083	37,104	37,124	37,145	37,165	37,185	37,204	37,224	37,243	37,263	37,282
% mNSCLC are EGFRmut	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%	12.0%
2L Pts. after Osimertinib in 1L	**33,259**	**33,279**	**33,298**	**33,318**	**33,337**	**33,356**	**33,375**	**33,393**	**33,412**	**33,430**	**33,448**	**33,466**	**33,484**	**33,502**	**33,519**	**33,536**	**33,553**
% of 1L	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%
Market penetration																	
Patients treated	-	-	-	-	-	-	-	83	1,750	4,602	8,354	11,372	14,030	13,968	13,905	13,843	13,780
% penetration	0%	0%	0%	0%	0%	0%	0%	0%	5%	14%	25%	34%	42%	42%	41%	41%	41%
Cost per month	6,300	6,426	6,555	6,686	6,819	6,956	7,095	7,237	7,381	7,529	7,680	7,833	7,990	8,150	8,313	8,479	8,649
% growth	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Months of treatment	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Avg. cost of therapy ($)	37,800	38,556	39,327	40,114	40,916	41,734	42,569	43,420	44,289	45,174	46,078	47,000	47,940	48,898	49,876	50,874	51,891
Patients on therapy	-	-	-	-	-	-	-	83	1,750	4,602	8,354	11,372	14,030	13,968	13,905	13,843	13,780
Sales ($M)	-	-	-	-	-	-	-	4	78	208	385	534	673	683	694	704	715

Source: Rodman & Renshaw Esimates

Valuation and Risks

Our Buy rating and $12 price target are driven by a risk-adjusted net present value analysis of the utility of ENV105 in: (1) metastatic castration-resistant prostate cancer patients who are failing first-line androgen receptor inhibition therapy (late-2028/early-2029 launch; ~$5.5B peak sales in 2034-35; 50% POS; contributes ~$9 to our PT;) and (2) EGFR-mutated NSCLC after frontline osimertinib failure (late-2029/early-2030 launch; ~$1.1B peak sales in 2035-36; 45% POS; contributes ~$2 to our PT). We also account for a modest risk-adjusted royalty contribution from a potential commercialization partner in ex-US regions (contributes ~$1 to our PT). Given Kairos' current cash position and the requirement to raise additional cash to be able to conduct registration trials in one or more indications, we apply an 18% discount rate. Our assumptions are subject to change if warranted by the availability of new information. Potential impediments to our rating and price target are outlined below:

- Kairos will require substantially more capital in order to execute any or all clinical programs to develop products in its portfolio. Capital may come in a number of ways, including the sale of equity, partnerships with larger pharmaceutical companies, or the outright sale of one or more products within their portfolio. However, there is no guarantee may be able to raise sufficient capital.
- Clinical trials with compounds owned by Kairos may not be successful in clinical development.
- Regulatory authorities may not approve a Kairos compound despite what might be considered a successful clinical program.
- Products developed clinically by Kairos may be successful through development but may face significant competition commercially and may not be able to generate sufficient revenue to offset expenses.
- Kairos may not be able to generate a profit.
- Kairos may not be successful at defending its intellectual property if it is challenged by another company.

Company description

Kairos Pharma is a clinical-stage company engaged in the development of novel and transformative drug therapies that target drug resistance and checkpoints of immune suppression in cancer. The science underlying the intellectual property was developed at Cedars-Sinai Medical Center. Headquartered in Los Angeles, CA, Kairos was founded by Dr. John S Yu, Professor and Clinical Chief of Neurosurgery and Director of the Brain Tumor Center at Cedars-Sinai Medical Center.

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RETURN ASSESSMENT

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.

Market Perform (Neutral): The common stock of the company is expected to mimic the performance of a passive index comprised of all the common stock of companies within the same sector.

Market Underperform (Sell): The common stock of the company is expected to underperform a passive index comprised of all the common stock of companies within the same sector.

Related Companies Mentioned in this Report as of December 18, 2024

Company	Ticker	Rodman & Renshaw Rating	12 Month Price Target	Price
Kairos Pharma, Ltd.	KAPA	Buy	$12.00	$1.66

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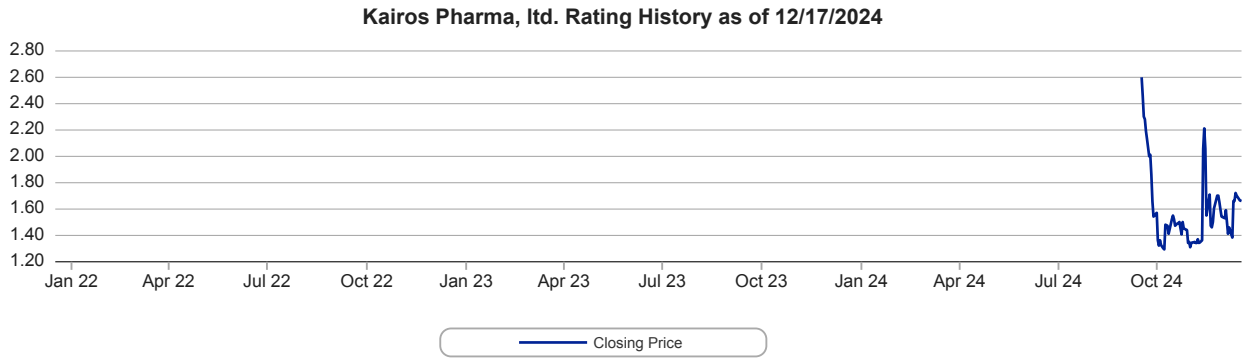

Distribution of Ratings Table as of December 18, 2024				
			IB Service/Past 12 Months	
Ratings	Count	Percent	Count	Percent
BUY	59	90.77%	4	6.78%
HOLD	5	7.69%	0	0.00%
SELL	1	1.54%	0	0.00%
NOT RATED	0	0.00%	0	0.00%

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