LAVERDIA™-CA1

verdinexor

Breakthrough Oral Treatment *for* Canine Lymphoma

Now FDA Contionally Approved

ANIVIVE

LAVERDIA™-CA1
verdinexor

The First Oral Treatment
Conditionally Approved by the FDA
for Canine Lymphoma

* Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-526

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

IMPORTANT SAFETY INFORMATION:
LAVERDIA-CA1 (verdinexor) is conditionally approved for the treatment of lymphoma in dogs. NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. CHILDREN SHOULD NOT COME INTO CONTACT WITH LAVERDIA-CA1. Children should not come in contact with the feces, urine, saliva, and vomit of treated dogs. View full product label for complete safety information. The most commonly reported adverse reactions in dogs include anorexia, weight loss, vomiting, diarrhea, and lethargy. Please see package insert or visit anivive.com for full prescribing information.

New first-in-class
SINE technology

Targeted

Kills cancer cells at the nuclear core, sparing healthy ones[1]

Effective*

Proven efficacy in all types of canine lymphoma[2,3]

Safe

Studies show only mild or moderate side effects[2,3]

Convenient

Twice weekly at-home oral administration increases compliance

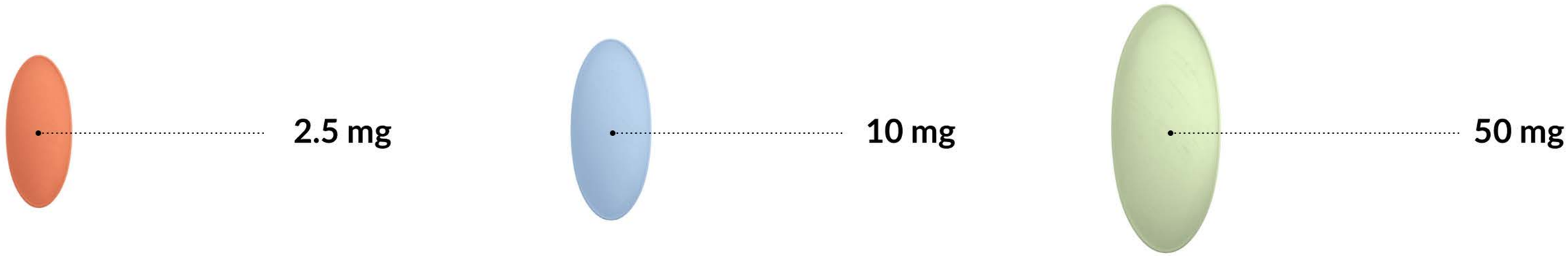
Affordable

Priced to expand your options and treat more patients

Expanding Access to Cancer Care

LAVERDIA-CA1 is an antineoplastic treatment with a novel mechanism that induces apoptosis and blocks proliferation of lymphoma cells while sparing healthy cells.

Clinical studies have demonstrated efficacy* against B-cell and T-cell lymphoma—in both naïve and relapse cases.



Easily incorporate LAVERDIA-CA1 into lymphoma treatment protocols for all types of patients:

Newly Diagnosed

Initial therapy when multi-agent or other treatment is declined due to cost or side effect concerns

Relapse

Rescue therapy when multi-agent or other treatment fails

Palliative

Prescribed for patients that traditionally choose steroid-only palliative care

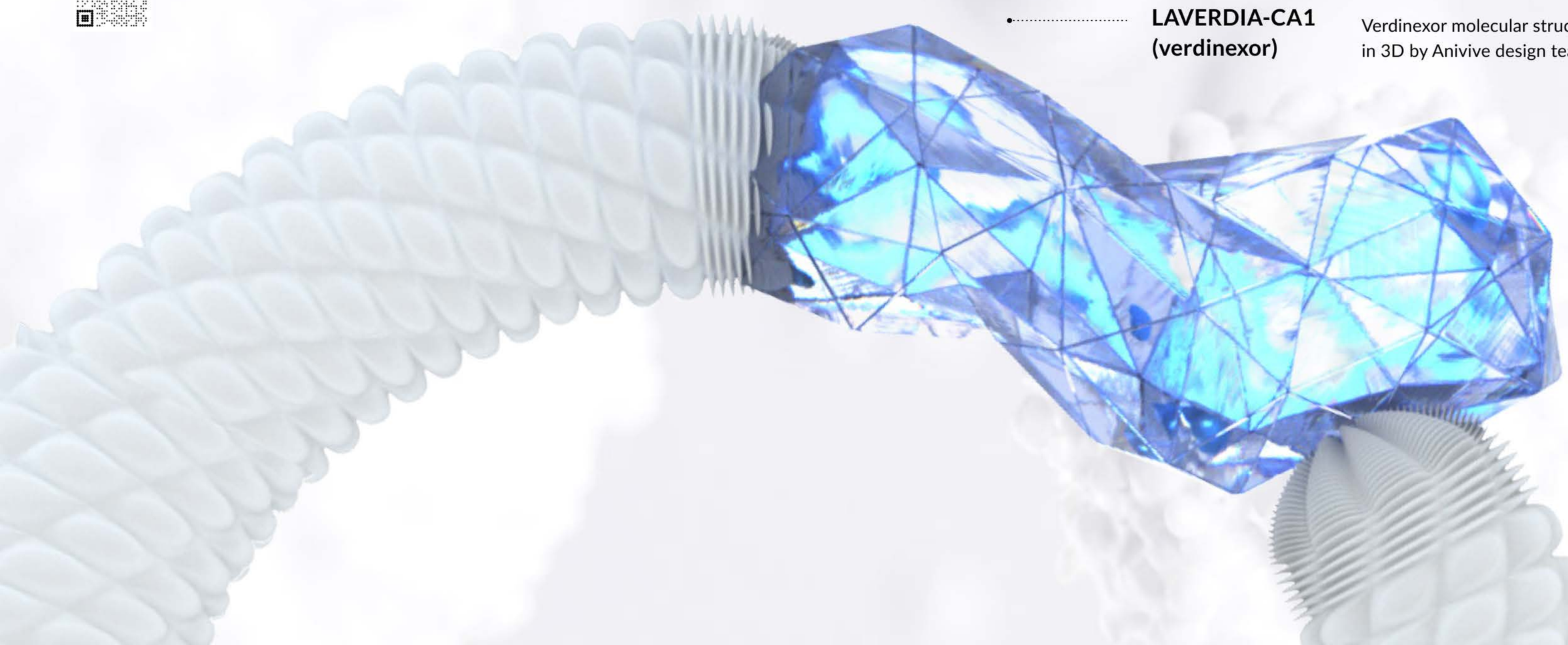
LAVERDIA-CA1 (verdinexor) A New Generation of XPO1 Inhibitor [4,5,6]

LAVERDIA-CA1 is a Selective Inhibitor of Nuclear Export (SINE) that binds to XPO1, blocking the transport of tumor suppressor proteins, arresting the cell cycle to inhibit lymphoma cell growth and induce apoptosis.

Watch how it works
anivive.com/laverdia

LAVERDIA-CA1 (verdinexor)

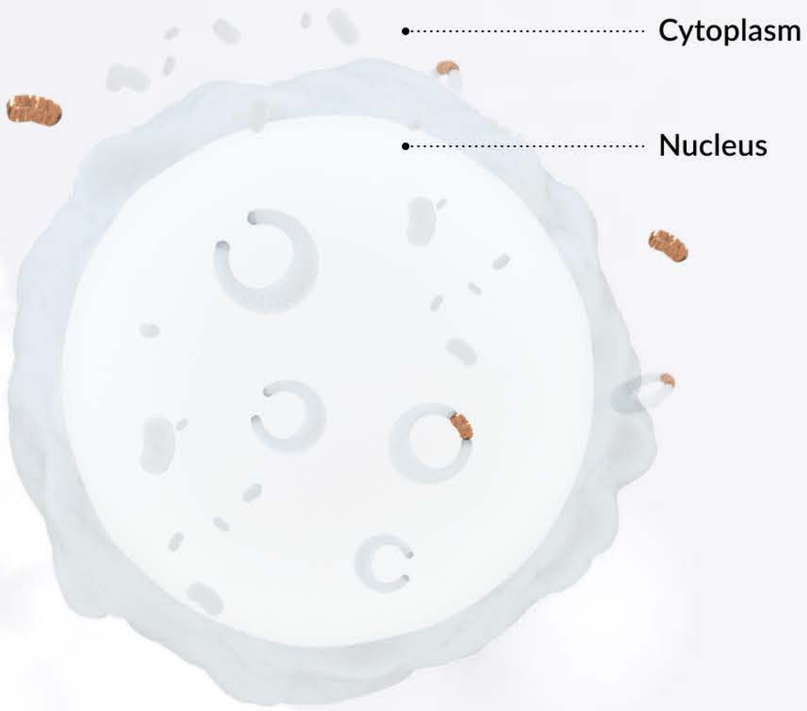
Verdinexor molecular structure in 3D by Anivive design team



Lymphoma Cells Overproduce XPO1s

LAVERDIA-CA1 Blocks XP01

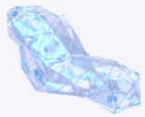
Lymphoma Cells Quickly Die



XPO1s

XP01s enable cancer cells to grow uncontrolled by exporting tumor suppressor proteins (TSPs) out of the cell nucleus

XPO1 is the sole nuclear exporter of several major tumor suppressor and growth regulatory proteins (GRPs), including p53, Rb1, and p27 among others. [7,8,9]



LAVERDIA-CA1

XPO1 inhibition results in nuclear retention and reactivation of TSPs leading to selective induction of apoptosis of lymphoma cells

Binds to XPO1s and selectively inhibits nuclear export of TSPs. This binding functionally inactivates XPO1 and targets the protein for proteasome degradation[7], resulting in restoration of TSPs cellular localization and function. The binding is slowly reversible, contributing to relatively low toxicity for healthy cells.[10]

TSPs

Healthy cells are spared[1] in this process while TSPs accumulate in lymphoma cells and cause apoptosis

TSPs (Tumor Suppressor Proteins) act inside the cell nucleus to suppress tumor growth.

LAVERDIA-CA1 (verdinexor) Treatment Algorithm for Canine Lymphoma

Lymphoma Diagnosis → **Discuss Referral and Treatments** → **Recommend Referral**

Recommend Referral → **Treated at Specialist**

Initial Therapy
Use in naïve patients when CHOP or other cytotoxic therapies are declined

Rescue Therapy
Use in relapse patients when CHOP or other therapies stop working or must be stopped due to side effects

Integrated Therapy
Easily integrate into your existing lymphoma treatment protocol

Decline Referral → **Treated at Primary Care Veterinarian**

Newly Diagnosed Patients
Use as treatment for patients who decline a specialist referral or have concerns about the side effects of traditional chemotherapy

Relapse Patients
Use as rescue therapy post CHOP or other chemotherapy initiated by specialist to provide ongoing care

Palliative Care Patients
Use as targeted therapy for patients who otherwise choose palliative care

Naïve

Relapse

Peer-Reviewed Publications

Read the clinical research on LAVERDIA-CA1 and SINE technology

162
publications on
SINE technology

14
specific to
verdinexor

Access these articles at **anivive.com/SINE**

Proven Efficacy Against All Types of Canine Lymphoma [2,3,11]

LAVERDIA-CA1 efficacy was established in a study with 58 client-owned dogs with B- or T-cell lymphoma, naïve cases or in first relapse after completing a single or multi-agent chemotherapy regimen. The study included dogs of varying breeds, weights, and genders with the majority of the dogs having stage III lymphoma.

THE OHIO STATE UNIVERSITY

Evaluation of the Novel, Orally Bioavailable Selective Inhibitor of Nuclear Export (SINE) KPT-335 (Verdinexor) in Spontaneous Canine Cancer: Results of Phase I and Phase II Clinical Trials

Abstract P1090

Cheryl A. London[1], Luis Feo Bernabe[1], Sandra Barnard[1], William C. Kisseberth[1], Antonella Borgatti[2], Mike Henson[2], Heather Wilson[3], Kiersten Jensen[2], Daisuke Ito[2], Jaime F. Modiano[2], Misty D. Bear[1], Michael L. Pennell[4], Jean-Richard Saint-Martin[5], Dilara McCauley[5], Michael Kauffman[5], Sharon Shacham[5]

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Abstract

Background: Selective Inhibitors of Nuclear Export (SINE) transiently block CRM1/XPO1, the major nuclear export protein in cells, forcing nuclear retention of key tumor suppressor and growth regulatory proteins ultimately resulting in tumor cell death.

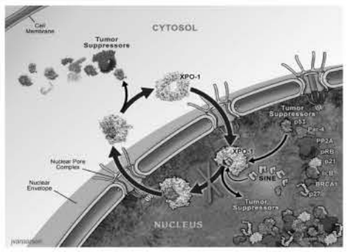
Aims: Here we evaluated the *in vitro* activity of SINE against canine tumor cell lines and investigate the biologic activity of verdinexor (KPT-335) in companion dogs with spontaneous cancers as proof of principle for human clinical studies.

Methods: Cytotoxicity assays were performed in several canine tumor cell lines including those derived from non-Hodgkin lymphomas (NHL). SINE compounds induced growth inhibition and apoptosis. NHL cell lines were particularly sensitive with IC_{50s} of 2 - 42 nM. Phase 1 and Phase 2 clinical trials of oral verdinexor were given to companion dogs with mast cell tumors, osteosarcomas, or NHL at doses of 1 – 1.75mg/kg.

Results: Seventeen dogs with NHL (naive or relapsed) were enrolled in a Phase 1 clinical trial. The maximum tolerated dose was 1.75 mg/kg, given orally twice weekly (Monday/Thursday). Objective responses include Partial Responses (PR n=2) and Stable Disease (SD n=7). Responders had a median Time To Progression (TTP) of 66 days (range 35-256). An additional six dogs with NHL were given verdinexor at a dose of 1.50 mg/kg Monday/Wednesday/Friday; clinical benefit was observed in 4/6 dogs with a median TTP for responders of 83 days (range 35-354). Toxicities were primarily GI-related including anorexia, weight loss, vomiting and diarrhea. Toxicities were manageable with supportive care, dose modulation and "low dose" prednisone. A subsequent Phase 2 study was performed in 58 dogs with either newly diagnosed or relapsed NHL. Verdinexor was administered at 1.25 - 1.50 mg/kg twice weekly (Monday/Thursday). The objective response rate was 34% (1 Complete Response, 19 PR) with an additional 33 dogs experiencing SD for ≥4 weeks. While the median TTP was approximately 5 weeks, 20 dogs (34%) remained on study drug for ≥8 weeks.

Conclusions: Dogs with T cell lymphoma, a form of disease considered to be biologically aggressive and challenging to treat with cytotoxic chemotherapy, had particularly good objective responses to single agent verdinexor (71% in naïve disease, 57% in relapsed disease). Verdinexor was well tolerated, with anorexia being the most common side effect. Furthermore, the quality of life did not significantly change over the study duration in all dogs enrolled (p=0.13), in dogs that remained on study for at least 28 days (p=0.66) or in dogs that remained on study for at least 56 days (p=0.52), indicating tolerability with both short- and long-term dosing. Together, these data provide robust evidence that the novel orally bioavailable XPO1 inhibitor verdinexor exhibits single agent biologic activity in a relevant spontaneous large animal model of human NHL. It is therefore likely that other SINE compounds, such as the closely related selinexor (KPT-330) will exhibit similar tolerability and biologic activity in humans. Preliminary data on selinexor in patients with advanced NHL support this.

Introduction



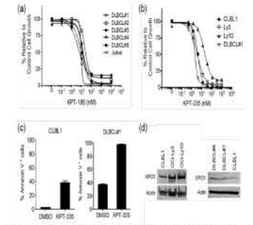
- XPO1is overexpressed in solid tumors and hematological malignancies and its levels are often correlate with poor outcomes
- XPO1 is the sole nuclear exporter of major tumor suppressor proteins (TSP)
- XPO1 inhibition results in nuclear restoration and reactivation of TSP leading to selective induction of apoptosis of cancer cells
- KPT-330 (a structurally analogous compound to Verdinexor) is currently being evaluated in Ph1 studies in solid and hematological malignancies

Materials and Methods

- *In vitro* assays: NHL cell lines, canine diffuse large B cell lymphoma cells, melanoma cell lines and osteosarcoma cell lines were treated with verdinexor (KPT-335) and assessed for effects on proliferation, cell survival, and XPO1 expression.
- Pharmacokinetics: Full PK was performed in healthy dogs to assess verdinexor oral bioavailability and determine the effects of feeding on drug absorption.
- Phase 1 study: Dogs (n=17) with NHL, MCT and metastatic OSA were treated with verdinexor in a planned 3 x 3 dose escalation starting at 1 mg/kg M/Th. An additional 6 dogs with NHL were entered into a dose expansion arm (1.5 mg/kg M/W/F). Dogs were evaluated weekly with physical exam, bloodwork (CBC, chemistry panel, coagulation panel) and response/toxicity assessment.
- Phase 2 study: Dogs with naïve or relapsed B or T NHL received verdinexor at 1.5 mg/kg or 1.25 mg/kg given M/Th or MWF. Evaluations were performed weekly for the first 4 weeks then every 2 weeks thereafter.

Results

Biologic Activity of SINE Compounds Against Canine Lymphoma Cells



Response of Canine Tumor Cell Lines to SINE

(A) Jurkat cells and primary canine DLBCL cells (sample #1-5) were cultured 72 hours with log serial dilutions of KPT-185 and the cell viability was analyzed **(B)** Human and canine DLBCL cells were cultured for 72 hours with serial dilutions of KPT-335 and cell viability was assessed. **(C)** CLBL1 cells and primary canine DLBCL cells (sample #1) were treated with verdinexor (KPT-335) for 24 hours and analyzed for apoptosis by flow cytometry. **(D)** Expression of XPO1 in human and canine DLBCL cell lines was assessed by SDS-PAGE and immunoblotting; β-actin was the control.

IC_{50} (± S.D.) of SINE for human and canine lymphoma cells

	KPT-335	KPT-185	KPT-185 trans
Jurkat	0.3	8.7 ± 0.7	>1000
OCI-Ly3	2.1 ± 1.3	24.1	NP
OCI-Ly10	41.8 ± 21.0	246.2	NP
CLBL1	8.5 ± 4.1	NP	NP
Canine DLBCLs	-	13.3 ± 6.2	-
DLBCL#1	2.0	13.1	NP
DLBCL#2	NP	9.0	NP
DLBCL#3	NP	12.2	NP
DLBCL#4	NP	4.9	NP
DLBCL#5	NP	21.6	>1000

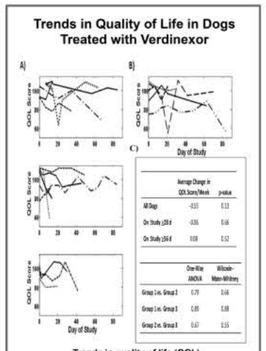
IC_{50}, 50% inhibitory concentration; DLBCL, diffuse large B-cell lymphoma; NP, not performed

Pharmacokinetics of Verdinexor in Healthy Dogs

Parameter	KPT-335 at1.5 mg/kg
Dose (mg/kg)	
Mean	1.46
SD	0.0542
SEM	0.0221
C_{max} (ng/mL)	
Mean	253
SD	88.3
SEM	36.1
T_{max} (hr)	
Mean	3.83
SD	2.71
SEM	1.11
$t_{1/2}$ (hr)	
Mean	3.88
SD	1.47
SEM	0.602
AUC_{0-t} (h*ng/mL)	
Mean	1810
SD	216
SEM	88.2
AUC_{0-Inf} (h*ng/mL)	
Mean	1760
SD	223
SEM	90.9

A single dose of 1.5 mg/kg verdinexor was administered to healthy beagle dogs 30 minutes after a meal. Plasma samples were taken over 24 hrs to assess drug levels.

Trends in Quality of Life in Dogs Treated with Verdinexor



Trends in quality of life (QOL)

An overall score was created based on answers to questions on the QOL questionnaire. These are represented graphically where each line represents a patient (**A** and **B**). Using linear mixed models, the overall QOL did not change significantly in dogs treated in either the (**A**) dose escalation portion (p=0.64) or (**B**) dose expansion portion (p=0.47) of the Phase 1 study. **(C)** In the Phase 2 study, the QOL did not change significantly in all dogs enrolled, dogs that remained on study for at least 28 days, or dogs that remained on study for at least 56 days. There was also no difference in QOL among dosing groups (Group 1: 1.5 mg/kg 3 times/week; Group 2: 1.25 m/kg 3 times/week; Group 3: 1.25 mg/kg 2 times/week)

Biologic Activity of Verdinexor in Canine NHL & Duration of Response

Phase 1	N	PR/CR	Clinical Benefit	Duration of Benefit
Dose Escalation	14	2 (14%)	9 (64%)	66 days (35-256)
Dose Expansion	6	2 (33%)	4 (67%)	83 days (35-354)
Phase 2				
All	58	20 (34%)	32 (55%)	71 days (21-273)
Naive B	28	8 (29%)	16 (57%)	71 days (28-195)
Relapse B	14	4 (29%)	6 (43%)	70 days (23-214)
Naive T	7	4 (57%)	5 (71%)	42 days (21-273)
Relapse T	7	4 (57%)	5 (71 %)	72 days (30-194)

Clinical benefit (CB) includes dogs with SD through D28 (with no PD events prior to D28) and PR/CR at any time during the study. Duration of benefit = time on study for all dogs with SD > 14 days or PR/CR

Dog	Phenotype	Naive or Relapse	OR	Duration of CR/PR (days)	Time to Tumor Progression (days)	Study Duration (days)
01-01	B-cell	Naive	PR	14	70	126
01-03	B-cell	Naive			114	121
01-05	B-cell	Naive			73	80
01-06	B-cell	Naive	PR	14	70	195
01-07	T-cell	Relapse	PR	49	72	72
01-12	B-cell	Naive			71	85
01-13	B-cell	Relapse			112	112
01-14	T-cell	Relapse			56	56
02-01	B-cell	Naive	PR	21	105	105
02-05	T-cell	Relapse	CR	152	194	194
03-01	B-cell	Naive			21	67
03-04	B-cell	Naive	PR	36	71	71
04-01	B-cell	Relapse	PR	13	20	56
06-02	T-cell	Naive	PR	36	62	119
06-03	T-cell	Naive	PR	126	244	273
07-05	T-cell	Relapse	PR	21	42	103
08-01	B-cell	Naive	PR	43	71	71
08-05	B-cell	Naive	PR	98	182	182
08-06	B-cell	Relapse			84	84
08-07	B-cell	Relapse	PR	45	112	214

Conclusions

- These data indicate that a proportion of dogs with both B and T NHL, either naïve or relapsed, benefit from verdinexor treatment as evidenced by both objective response to therapy and prolonged disease stabilization; dogs with T cell disease, typically refractory to therapy, seem to experience significant benefit.
- Verdinexor exhibits an excellent safety profile over long-term dosing with primarily grade 1 and 2 gastrointestinal toxicities that are readily managed with concomitant medications and no negative impact on quality of life during therapy.
- Selinexor (KPT-330 – a structurally analogous compound to verdinexor, KPT-335) is currently in human clinical trials and has demonstrated similar activity and tolerability in hematopoietic neoplasia (NCT01607892) further validating XPO1 as a relevant target for therapeutic intervention across multiple species.

(See next page for the table information)

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Clinical Response[11]

Phase 2 Study	N	PR/CR	Clinical Benefit	Duration of Benefit
All	58	20 (34%)	32 (55%)	71 days (21-273)
Naïve B	28	8 (29%)	16 (57%)	71 days (28-195)
Relapse B	14	4 (29%)	6 (43%)	70 days (23-214)
Naïve T	7	4 (57%)	5 (71%)	42 days (21-273)
Relapse T	7	4 (57%)	5 (71%)	72 days (30-194)

Clinical Benefit (CB) includes dogs with Stable Disease through D28 (with no Progressive Disease events prior to D28) and Partial Response/Complete Response at any time during the study. Duration of Benefit = time on study for all dogs with Stable Disease > 14 days or PR/CR.

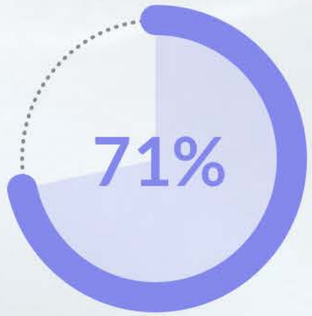
Efficacy Data for Dogs Remaining on Study Past Day 56[11]

Dog	Phenotype	Naïve or Relapse	Objective Response	Duration of CR/PR (days)	Time to Tumor Progression (days)	Study Duration (days)
01-01	B-cell	Naïve	PR	14	70	126
01-03	B-cell	Naïve			114	121
01-05	B-cell	Naïve			73	80
01-06	B-cell	Naïve	PR	14	70	195
01-07	T-cell	Relapse	PR	49	72	72
01-12	B-cell	Naïve			71	85
01-13	B-cell	Relapse			112	112
01-14	T-cell	Relapse			56	56
02-01	B-cell	Naïve	PR	21	105	105
02-05	T-cell	Relapse	CR	152	194	194
03-01	B-cell	Naïve			21	67
03-04	B-cell	Naïve	PR	36	71	71
04-01	B-cell	Relapse	PR	13	20	56
06-02	T-cell	Naïve	PR	36	62	119
06-03	T-cell	Naïve	PR	126	244	273
07-05	T-cell	Relapse	PR	21	42	103
08-01	B-cell	Naïve	PR	43	71	71
08-05	B-cell	Naïve	PR	98	182	182
08-06	B-cell	Relapse			84	84
08-07	B-cell	Relapse	PR	45	112	214

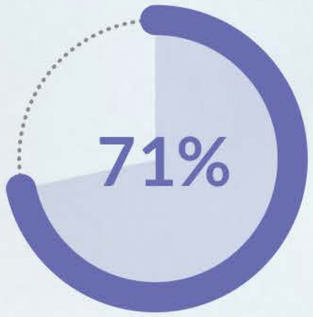
Overall Clinical Benefit

B-cell naïve

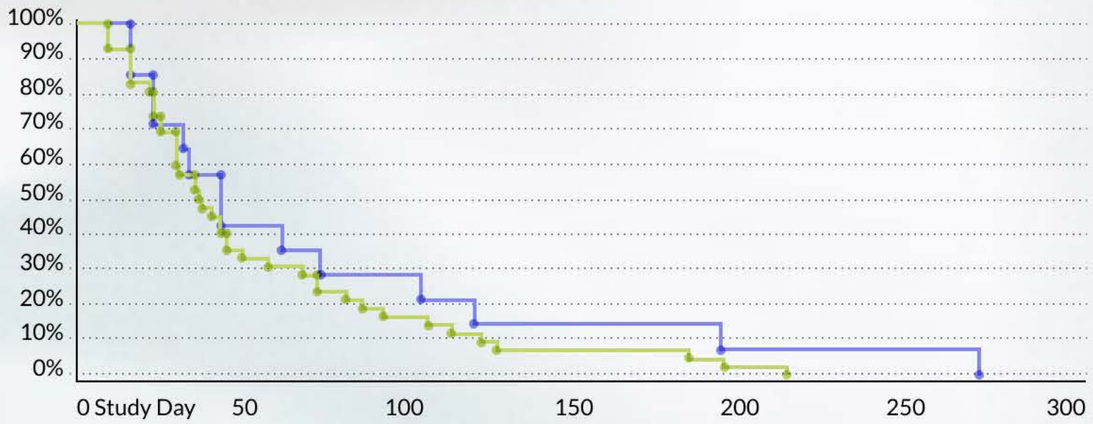
B-cell relapse



T-cell naïve



T-cell relapse



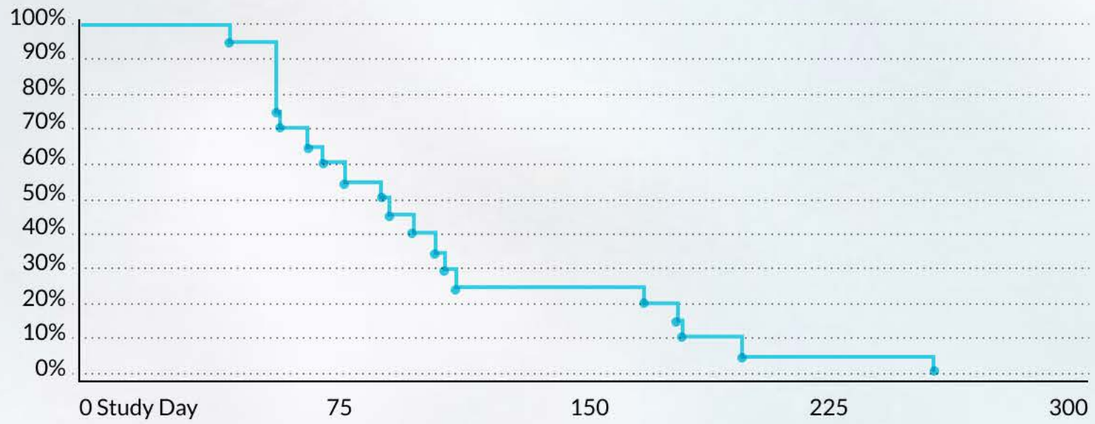
Days on Study n=56* B-cell (N=42) T-cell (N=14) Event

67%
@28 days

29%
@56 days

** Two of treated dogs were not immunophenotyped.*

At day 28, 67% (39/58) of dogs continued on study. A subset (17/58, 29%) of the overall enrolled population had a TTP of at least 56 days.



Days on Study at Least 56 Days n=17 All Dosed Dogs (N=17) Event

82%
@75 days

65%
@100 days

41%
@120 days

29%
@180 days

12%
@200 days

Of these 17 dogs, 11 were naïve to treatment and 6 had relapsed lymphoma; 5 had T-cell lymphoma and 12 had B-cell lymphoma. 3 dogs—2 with T-cell lymphoma (1 naïve, 1 relapsed) and 1 with B-cell lymphoma (naïve)—had TTP of 182 days or longer.

Overall Quality of Life

A validated health related Quality of Life (QOL) form used to assess dogs during treatment demonstrated that the overall QOL did not decrease in dogs during treatment, supporting the notion that clinical toxicities associated with verdinexor are generally well tolerated.

LAVERDIA-CA1 has been shown to be well tolerated over both short and long term administration. In addition, quality of life scores for treated dogs did not diminish over time.[2]

See Package Insert for full safety information

LAVERDIA-CA1 (verdinexor) Generally Well Tolerated in Clinical Studies [2,3]

Convenient

- 95% of clinical study participants adhered to dosing requirements
- Most adverse reactions resolved spontaneously, or with supportive treatment, or dose modifications
- No dogs discontinued therapy as a result of side effects in clinical trials
- Low doses of prednisone were shown to reduce anorexia and gastrointestinal side effects[2]
- Schedule appointments for routine monitoring, periodic physical exams, and blood work as needed based on patient's response

Side Effects

- The most common adverse reactions included: anorexia, weight loss, vomiting, lethargy, and diarrhea. The majority of adverse reactions (95%) were Veterinary Cooperative Oncology Group (VCOG) grade 1 or 2. Side effects were effectively managed without hospitalization

LAVERDIA-CA1 Targeted Therapy

- Selective inhibitor of nuclear export (SINE) that binds to XPO1 in a slowly reversible manner [5,6]
- Induces cancer cell death while sparing non-malignant cells[12]

Scan to download the
Quality of Life Survey form

IMPORTANT SAFETY INFORMATION:
LAVERDIA-CA1 (verdinexor) is conditionally approved for the treatment of lymphoma in dogs. NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. CHILDREN SHOULD NOT COME INTO CONTACT WITH LAVERDIA-CA1. Children should not come in contact with the feces, urine, saliva, and vomit of treated dogs. View full product label for complete safety information. The most commonly reported adverse reactions in dogs include anorexia, weight loss, vomiting, diarrhea, and lethargy. Please see package insert or visit anivive.com for full prescribing information.

Purposefully Designed

Color Coated Tablets

Allows for safe at-home administration and easy identification of tablet strength.

Precise Dosing

Three tablet strengths allow for precise dosing for each patient to maximize the therapeutic benefit while minimizing side effects.

Convenient Oral Administration

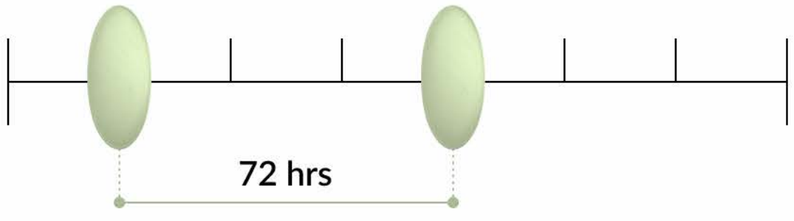
Initial Dosing: **1.25 mg/kg** given twice per week with at least 72 hours in between doses.

If tolerated after two weeks, increase the dose of LAVERDIA-CA1 to **1.5 mg/kg** twice per week with at least 72 hours between doses.

See **Package Insert** for full prescribing information

Easy Oral Administration
Twice Weekly

Safely administered in the comfort of home. Wear chemotherapy resistant gloves when handling LAVERDIA-CA1. See Client Information Sheet and Package Insert for detailed handling instructions.



Twice Weekly Administration
72 Hours Between Doses

Rapid Onset of Action

Feed Before Administering Dogs should be fed immediately before giving LAVERDIA-CA1. Time to maximum plasma concentration is between 1.1 and 2.5 hours post-dose under fed conditions.

Well Absorbed and Bioavailable

LAVERDIA-CA1 is well absorbed in dogs and achieves therapeutic levels (>0.5 to 1.0 µM) with doses of 1 to 3 mg/kg. There is a significant food effect on the pharmacokinetics of LAVERDIA-CA1 with a 3-fold and 5-fold increase in AUC and Cmax, respectively.

Developed by Leading Oncology Researchers and Clinicians

Defining New Protocols

Every member of the Anivive Oncology Advisory Board has extensive knowledge of LAVERDIA-CA1 (verdinexor) and is available to help you develop new lymphoma protocols for your hospital.

The Future of Cancer Care

The Advisory Board guided the accelerated development of LAVERDIA-CA1 and were principal investigators in clinical trials. They will continue ongoing research, defining new industry best practices to improve the future of cancer care.

LAVERDIA™-CA1

Starts with an "**L**" to acknowledge the significant contributions and tireless efforts of the oncologist who helped bring this new drug to life: **Dr. Cheryl London**.

Cheryl London
DVM, PhD, DACVIM (O)
Associate Dean
Professor
Tufts University

Principal Investigator
LAVERDIA-CA1 efficacy studies
"Verdinexor presents a paradigm shift in the treatment of lymphoma and has the potential to become routine 'standard of care' treatment for dogs."

Phil Bergman
DVM, PhD, DACVIM (O)
Director of Clinical Studies
VCA Animal Hospitals

Craig Clifford
DVM, MS, DACVIM (O)
Director of Clinical Studies
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