Pharmacodynamic Endpoint Assessment in Canine Oncology Trials

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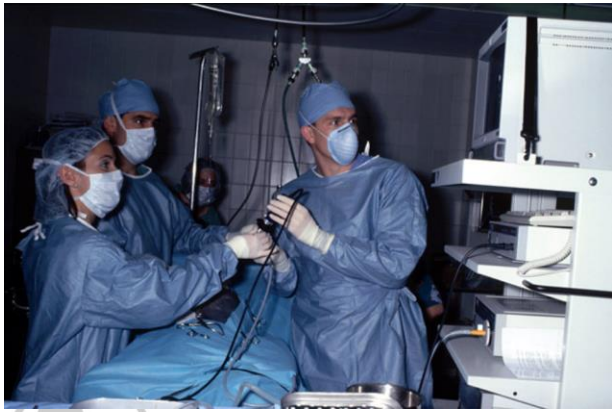
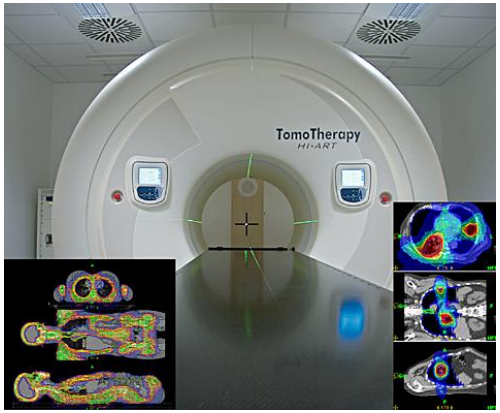
Conflict of Interest

Scientific Advisory Boards	MBC Pharma, VetDC; Taiga Biotechnologies
Paid Consulting	Zoetis; Novartis Animal Health
Sponsored Research	Zoetis; Novartis Animal Health; Nexvet; VetDC; Taiga Biotechnologies; Susavion
Financial Relationships	Veterinary Diagnostics Institute; TheragNOS; VetDC; CETYA Therapeutics; Calviri; Taiga Biotechnologies

Potential advantages - companion animal model

- Favorable body size
  - *Allows safe, repeated tissue or blood sample collection - ideal for validating non-invasive imaging techniques, validating target modulation*
  - *Commonality of imaging techniques*
  - *Drug delivery - aerosolized lung therapy, isolated perfusion*
  - *Radiation delivery*

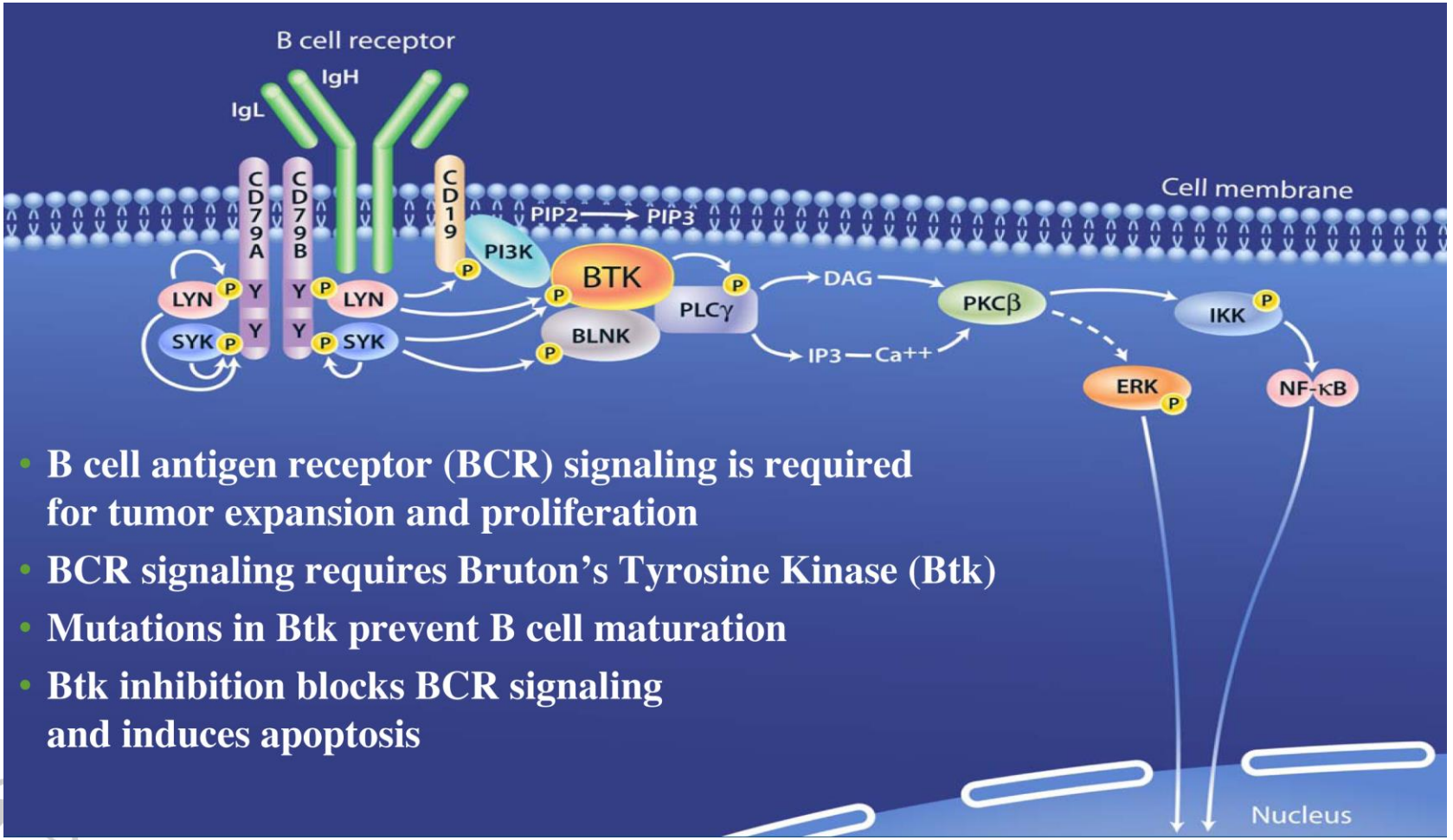




Potential Value

- Validation of target modulation *in tumor tissue* through serial biopsy
  - *PK-PD relationships*
  - *Correlations between tumor and surrogate PD endpoints*
- Validation of tumor-specific targeted delivery
- Investigations of potential predictive biomarkers

B Cell Receptor Signaling



- **B cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation**
- **BCR signaling requires Bruton's Tyrosine Kinase (Btk)**
- **Mutations in Btk prevent B cell maturation**
- **Btk inhibition blocks BCR signaling and induces apoptosis**

The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy

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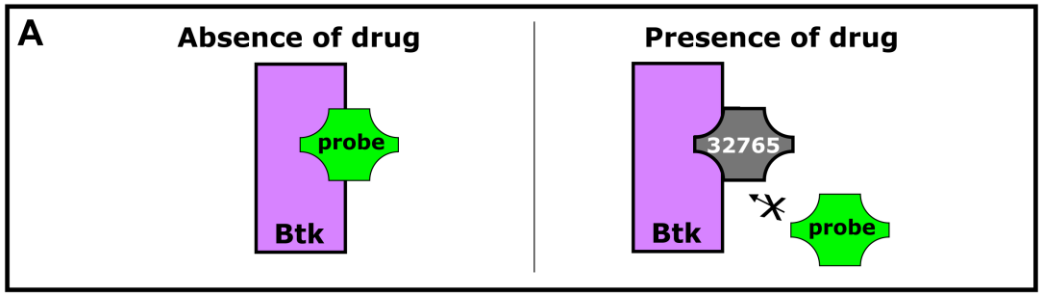

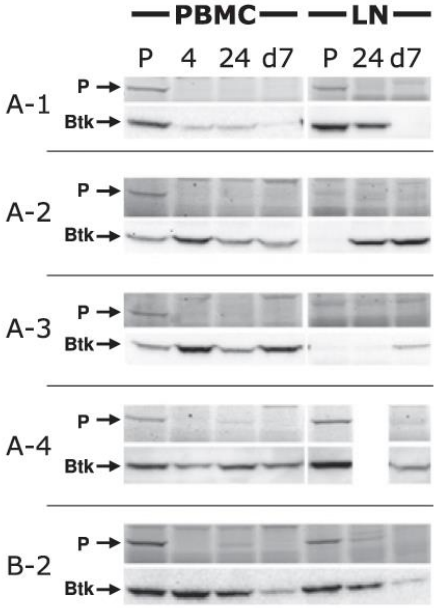

Table 1. Study summary of the effect of Btk inhibitor PCI-32765 in naturally occurring canine lymphomas

Dog	Stage	Histology	PARR (monoclonal BCR)	Previous Treatment	Dose, mg/kg	Outcome (RECIST)	Progression free interval, d	Decrease in tumor sums, %
A1	IIIa	NA	—	—	20	SD	28	10
A2	Va	NA	+	COP	20	PD	0	—
A3	IIIa	Follicular large cell	—	CHOP	20	SD	14	—
A4	IIIa	Diffuse immunoblastic	+	COP	20	PR	35	77
B1	IIIa	Diffuse immunoblastic	+	—	2.5/5.0/7.5	SD	21	—
B2	IIIa	Follicular large cell	+	—	2.5/5.0	PR	70	31
B3	IIIa	Diffuse immunoblastic	+	—	2.5	PD	0	—
B4	Va	Follicular large cell	+	—	2.5/5.0	PR	63	62

CR, complete response; NA, not applicable; PARR, PCR of antigen receptor rearrangement; PD, progressive disease; PR, partial response; SD, stable disease.

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Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

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ORIGINAL ARTICLE

ine Kinase Inhibitor Ibrutinib (PCI-32765) nt Activity in Patients With ractory B-Cell Malignancies

ph J. Buggy, Jeff P. Sharman, Sonali M. Smith, Thomas E. Boyd, Barbara Grant, hard R. Furman, Sara Rodriguez, Betty Y. Chang, Juthamas Sukbuntherng, amdy, Eric Hedrick, and Nathan H. Fowler

ticle doi: 10.1200/JCO.2012.44.4281

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ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stilgenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.

Challenges

- Target expression
  - *Is there a canine Btk homolog?*
  - *Do canine B cell lymphomas express Btk?*
  - *Is Btk active in canine B cell lymphoma?*
- Target modulation
  - *Cross-reactive antibodies*

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PLOS one

Launching a Novel Preclinical Infrastructure: Comparative Oncology Trials Consortium Directed Therapeutic Targeting of TNFα to Cancer Vasculature

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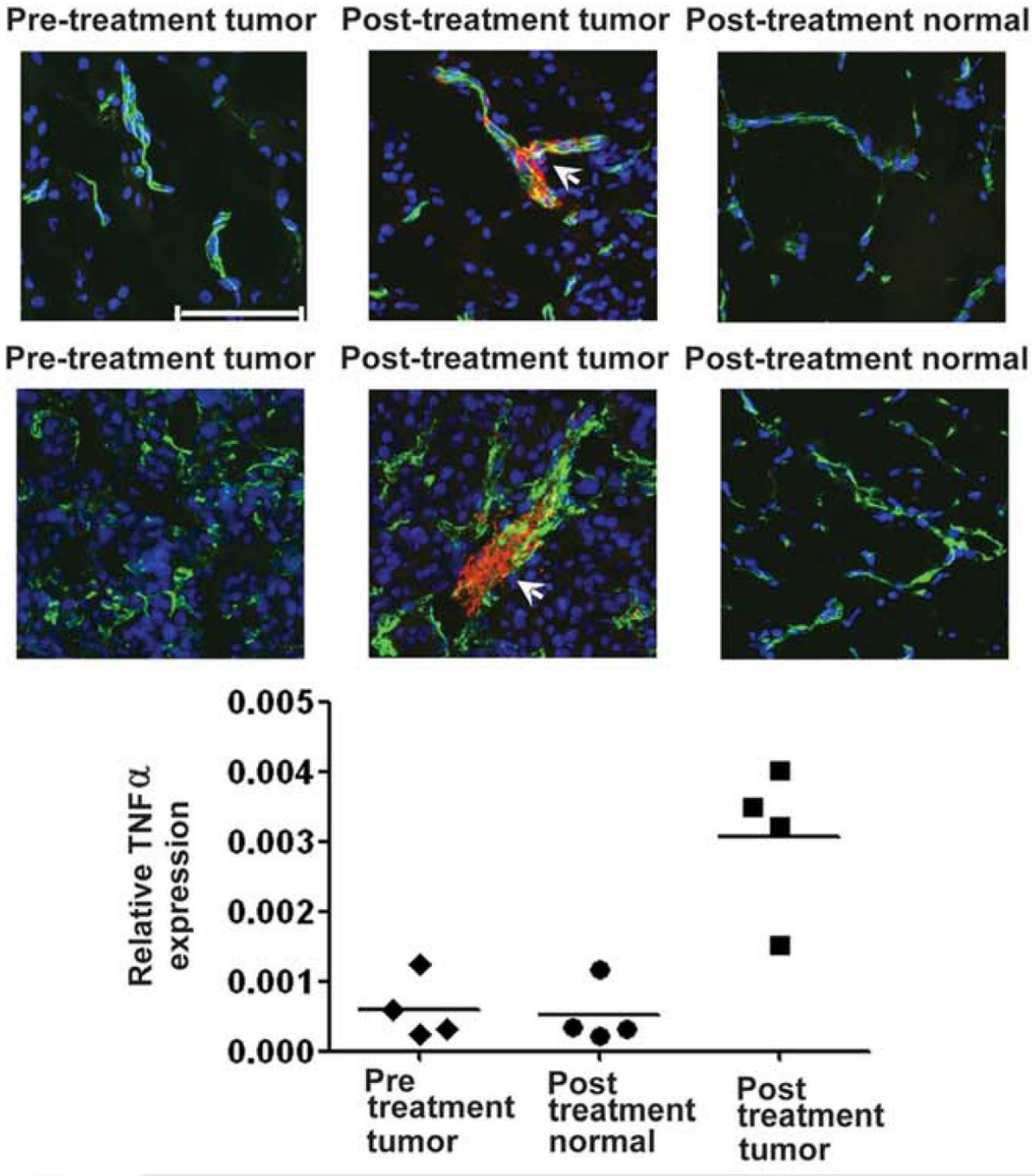
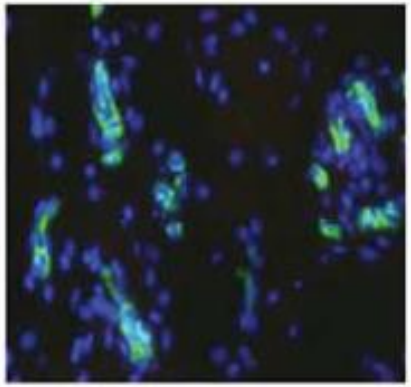
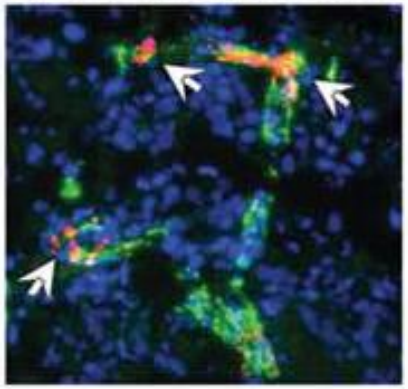
- Tumor necrosis factor (TNF) – potent pro-inflammatory, pro-apoptotic, anti-angiogenic cytokine but significant systemic toxicity
- Alpha$_V$ beta$_3$ expressed on “angiogenic” vasculature, can be targeted via RGD peptide motifs
- RGD-targeted AAV phage vector expressing TNF evaluated



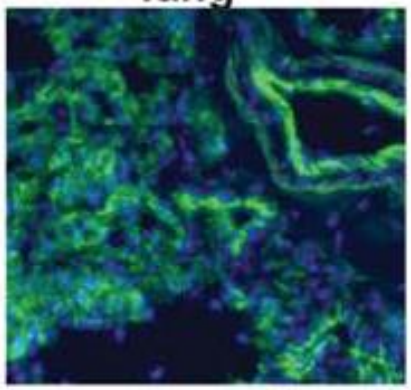
Pre-treatment tumor



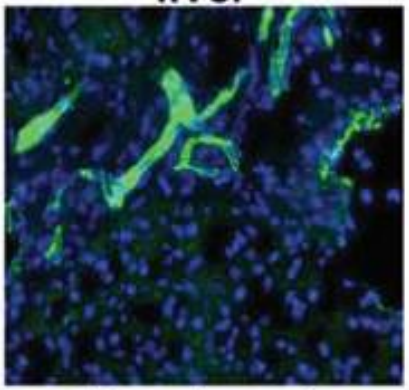
Post-treatment tumor



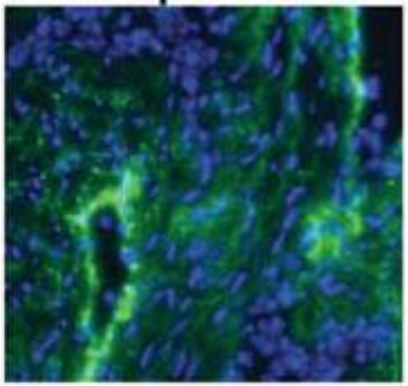
Post-treatment normal lung



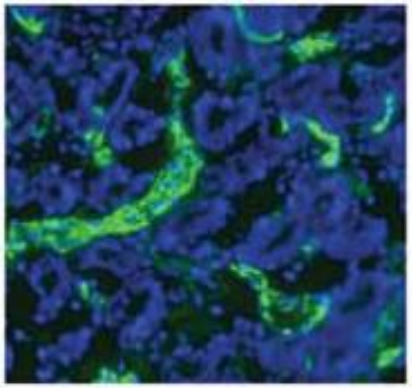
Post-treatment normal liver



Post-treatment normal spleen

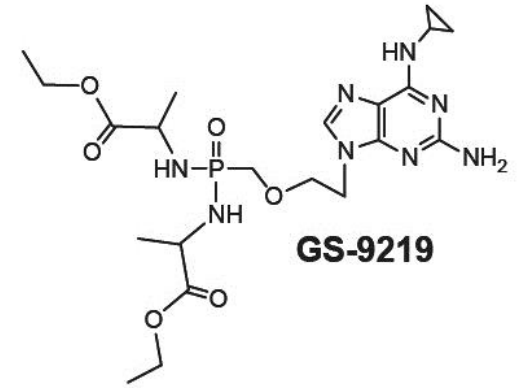


Post-treatment normal intestine

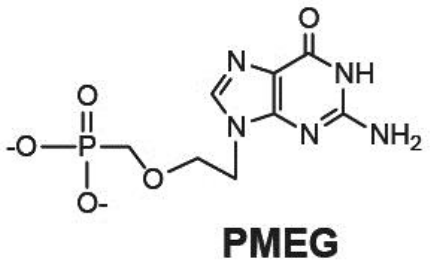


Rabacfosadine (TANOVEA™) (GS-9219, VDC-1101)

- Novel double prodrug of the anti-proliferative nucleotide analog 9-(2-phosphonylmethoxyethyl)guanine (PMEG)
- PMEG: known antiproliferative effects but severe DLTs when given systemically
- VDC-1101 effectively loads lymphoid cells while markedly reducing levels of PMEG in plasma and target organs of toxicity
- VDC-1101 inhibits proliferation of myeloid and lymphoid cell lines *in vitro*



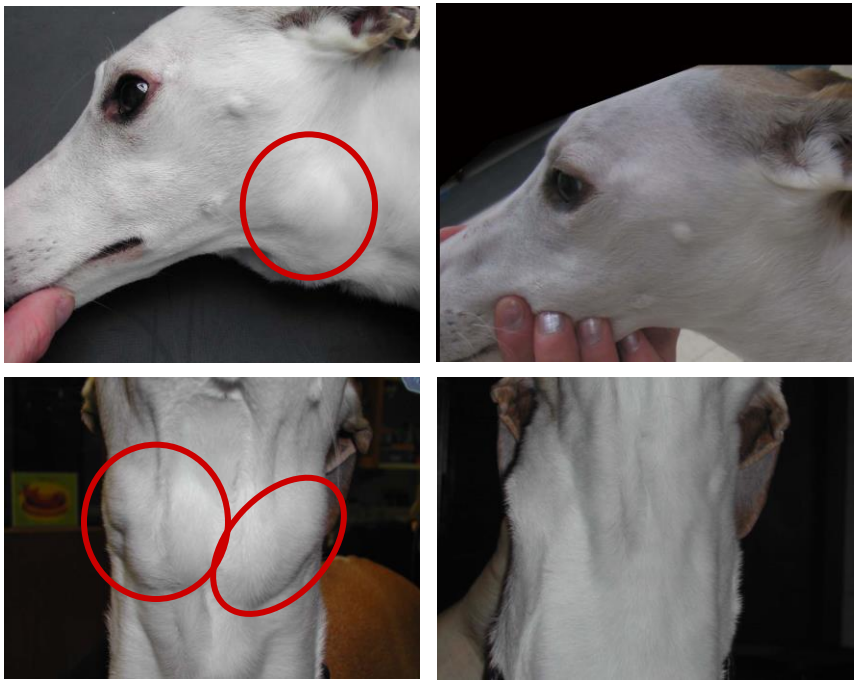
Hydrolysis
Deamination



Reiser H et al: **Clin Cancer Res** 14(9): 2824, 2008

Rabacfosadine – Efficacy Results in Dogs with NHL

Pre-treatment **Day 6 post-dose**



- Multiple schedules evaluated
- 30 of 38 dogs (79%) responded:
  - *23 CR (61%), 7 PR (18%)*
  - *All treatment-naïve dogs (n=17) responded*
  - *13/21 with previously treated, relapsed NHL responded (10 CR, 3 PR, 62%)*
- FRD = 128 days (99 days for pre-treated)
- Dogs completing 5 cycles in CR that relapsed upon termination of treatment were successfully reinduced by retreatment with rabacfosadine

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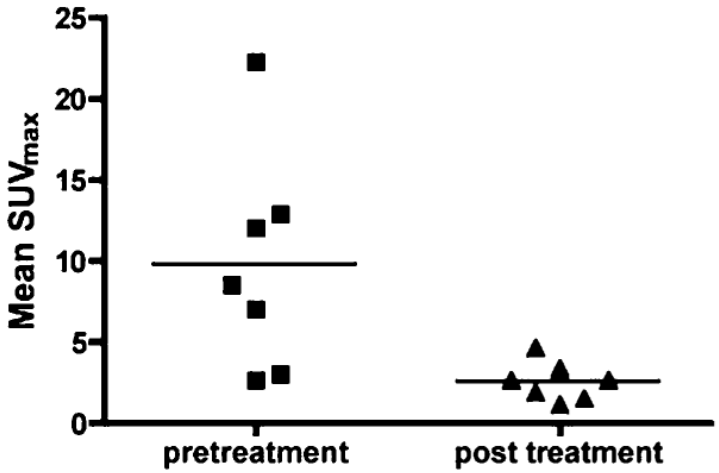
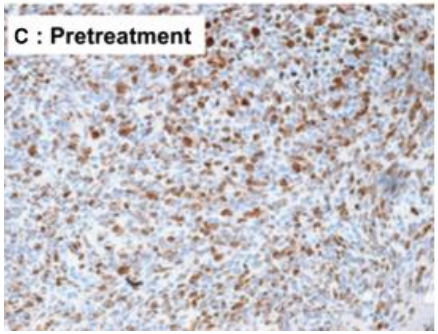
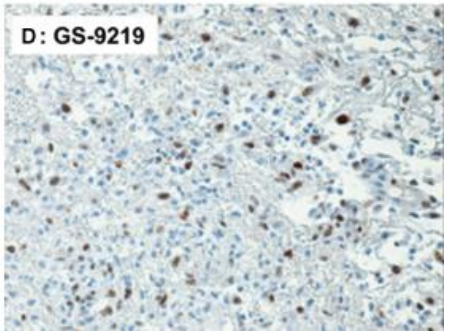
Vail D et al: **Clin Cancer Res** 15(10): 3503, 2009

^{18}F-fluorothymidine PET/CT







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Lawrence J et al: **Vet Radiol Ultrasound** 50(6): 660, 2009

Phase I Dose-Escalating Study of SU11654, a Small Molecule Receptor Tyrosine Kinase Inhibitor, in Dogs with Spontaneous Malignancies[1,2]

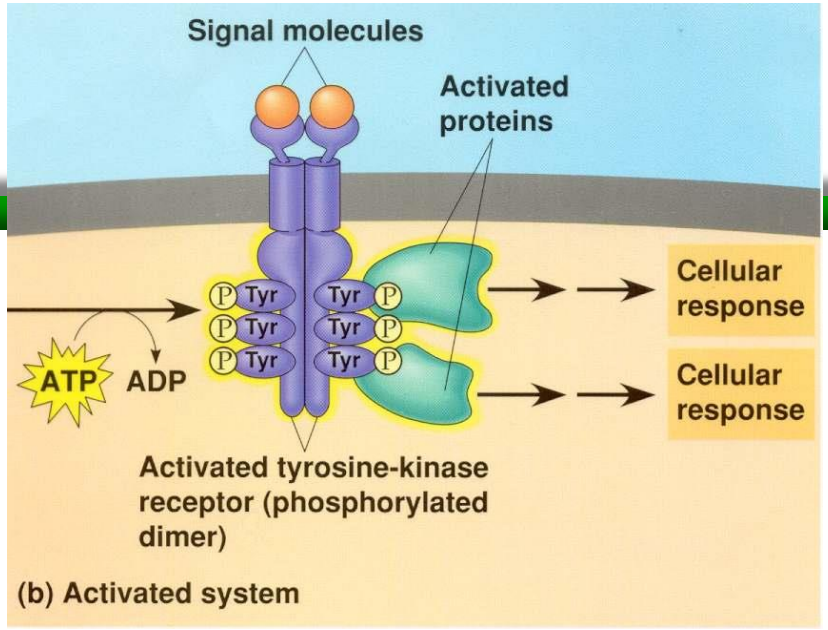
Cheryl A. London,[3] Alison L. Hannah, Regina Zadovoskaya, May B. Chien, Cynthia Kollias-Baker, Mona Rosenberg, Sue Downing, Gerald Post, Joseph Boucher, Narmada Shenoy, Dirk B. Mendel, Gerald McMahon, and Julie M. Cherrington

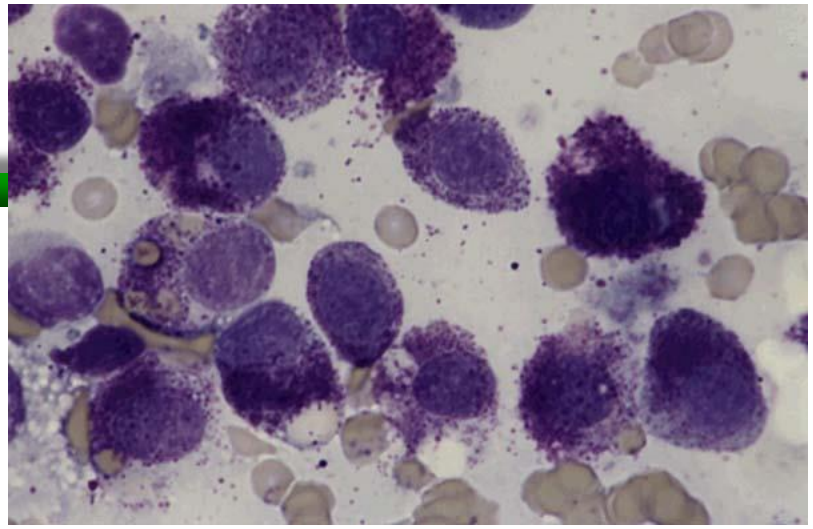
School of Veterinary Medicine, University of California, Davis, Davis, California 95616 [C. A. L., R. Z., M. B. C., C. K-B.]; Veterinary Cancer Referral Group, Los Angeles, California [M. R., S. D.]; Veterinary Cancer Referral Group, New York, New York [G. P.]; SUGEN, Inc., South San Francisco, California [A. L. H., N. S., D. B. M., G. M., J. M. C.]; and Pharmacia Animal Health, Kalamazoo, Michigan [J. B.]

Proof of Target for SU11654: Inhibition of KIT Phosphorylation in Canine Mast Cell Tumors

Nancy K. Pryer,[1] Leslie B. Lee,[1] Regina Zadovaskaya,[2] Xiaoming Yu,[1] Juthamas Sukbuntherng,[1] Julie M. Cherrington,[1] and Cheryl A. London[2]

[1]SUGEN, Inc., South San Francisco, California, and [2]School of Veterinary Medicine, University of California–Davis, Davis, California



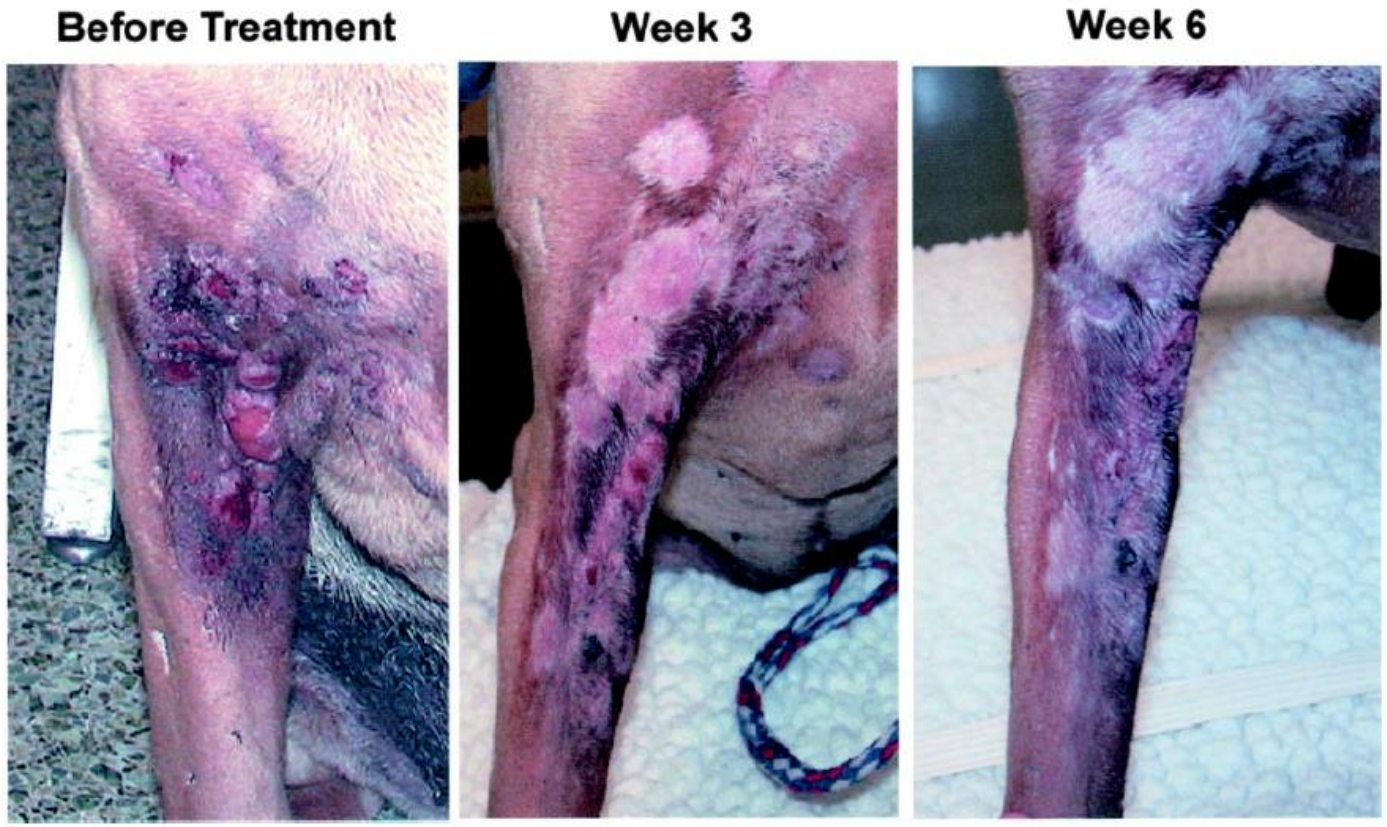


- KIT protein expressed on normal and malignant mast cells
- Mutations in juxtamembrane domain of *c-kit* gene, leading to constitutive activation, detected in 20-40% of canine MCT
- Similar activating mutations present in human gastrointestinal stromal tumor

Table 5 Response rate in MCT by mutation and lymph node disease

	Lymph node negative	Lymph node positive
Kit mutation negative	50% (2/4)	0% (0/7)
Kit mutation positive	100% (6/6)	60% (3/5)

b)



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London CA et al: **Clin Cancer Res** 9: 2755-68, 2003.

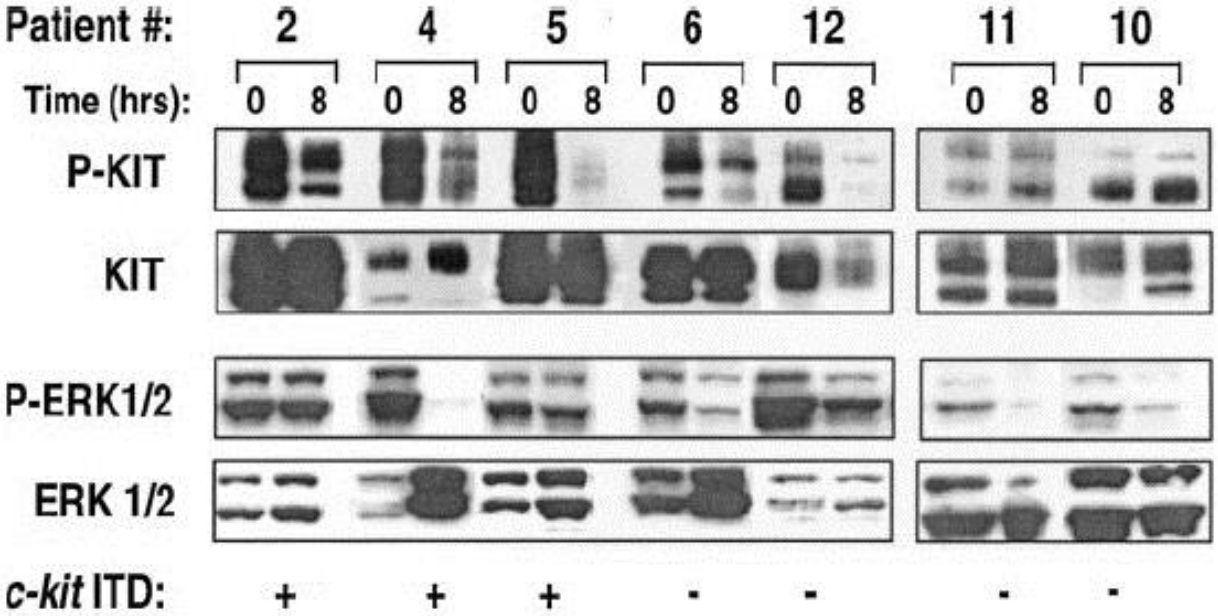
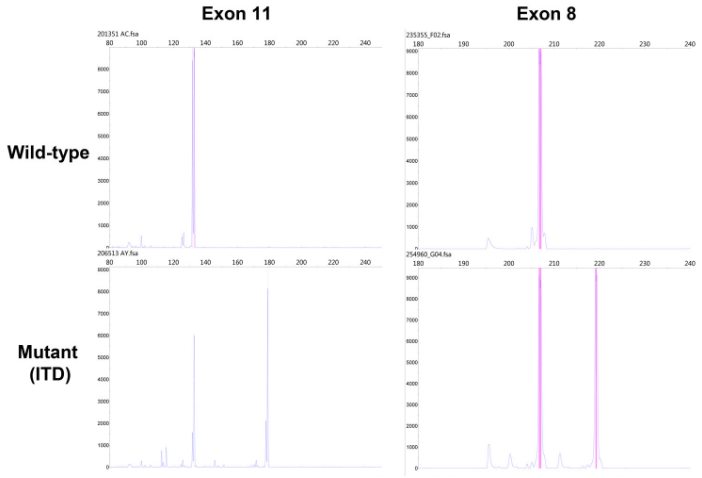
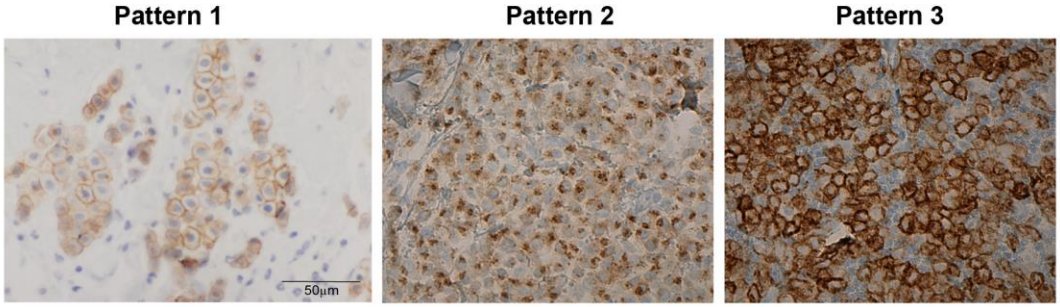


Fig. 2 Reductions in MCT phosphorylated KIT and phosphorylated ERK1/2 after a single dose of SU11654. Frozen tumor biopsies taken before SU11654 treatment (0 h) and after administration of a single dose of SU11654 (8 h) were immunoprecipitated with an antibody to KIT and probed by Western blot with an antibody to phosphotyrosine 721 KIT, then reprobed for total KIT. The five biopsy pairs on the *left* were scored as positive for target modulation, whereas the two on the *right* were scored as negative. Whole cell lysates from the same samples were analyzed by Western blot for phospho-ERK1/2 and then reprobed for total ERK1/2.

Pryer NK et al: **Clin Cancer Res** 9: 5729-34, 2003.

c-Kit Mutation and Localization Status as Response Predictors in Canine Mast Cell Tumors Treated with Toceranib or Vinblastine: A Response-Adaptive Randomized Trial





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Acknowledgements