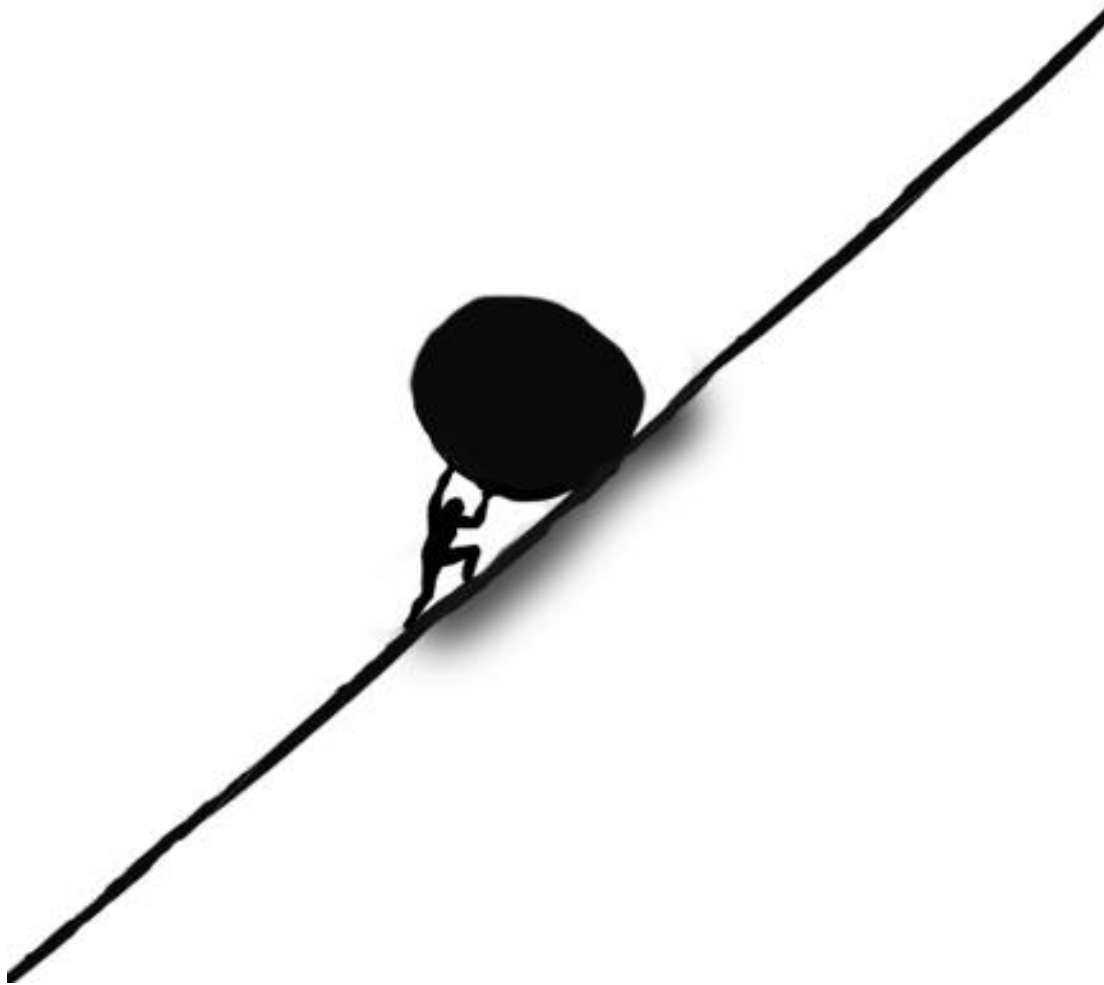


Evaluation of GS 9219/VDC-1101 in Dogs with Hematological Malignancies

Daniel B. Tumas
Gilead Sciences, Inc
June 9th, 2015

Drug discovery and development is difficult



How can we work together?



**Drug Discovery &
Development in
Humans**



**Role of Clinical Studies
in Pet Dogs with
Naturally Occurring
Tumors**

What is the goal?

**The goal is to be transformative.
Significantly move the Rock.**

Does the paradigm enable success?

**Drug Discovery &
Development in
Humans**

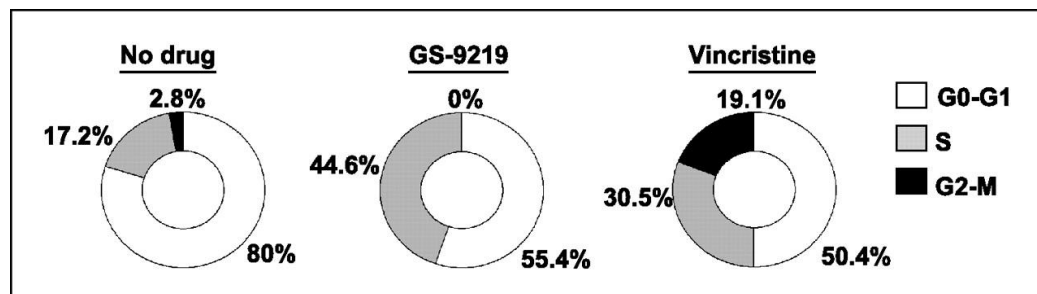
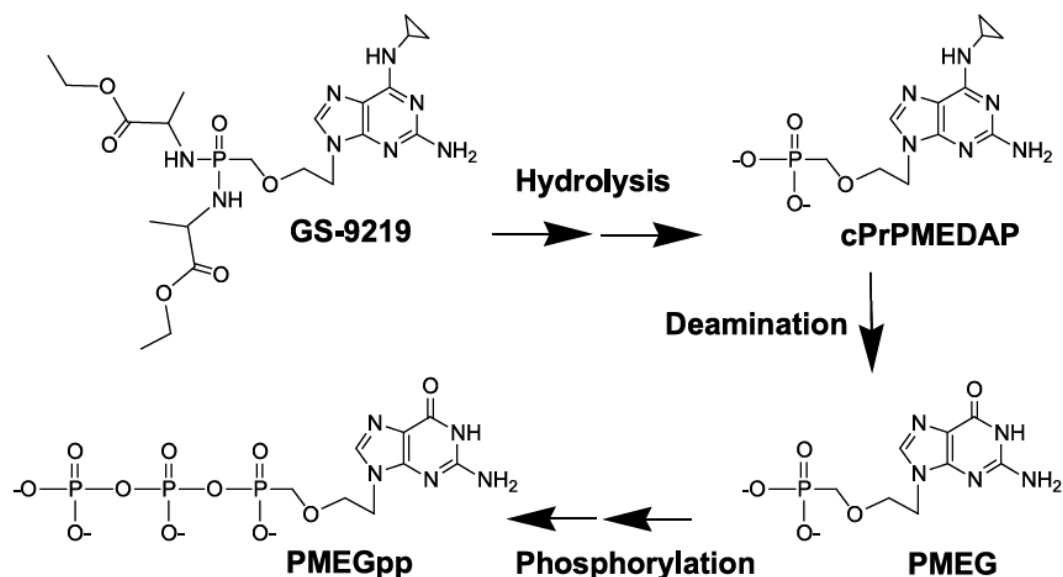


**Role of Clinical Studies
in Pet Dogs with
Naturally Occurring
Tumors**

What scenarios are most likely to meet the goal - move the Rock?

- 1. Cancers for which the outcome in dogs is predictive for humans.**
- 2. Proof of Concept for a novel therapeutic.**
- 3. Human cancers with high unmet need that are recapitulated in dogs**
- 4. Rational evaluation of novel combinations.**
- 5. High Potential for benefit - humans and/or dogs - Win-Win?**

GS 9219 - anti-proliferative nucleotide analog pro-drug



EC₅₀ inhibition of proliferation

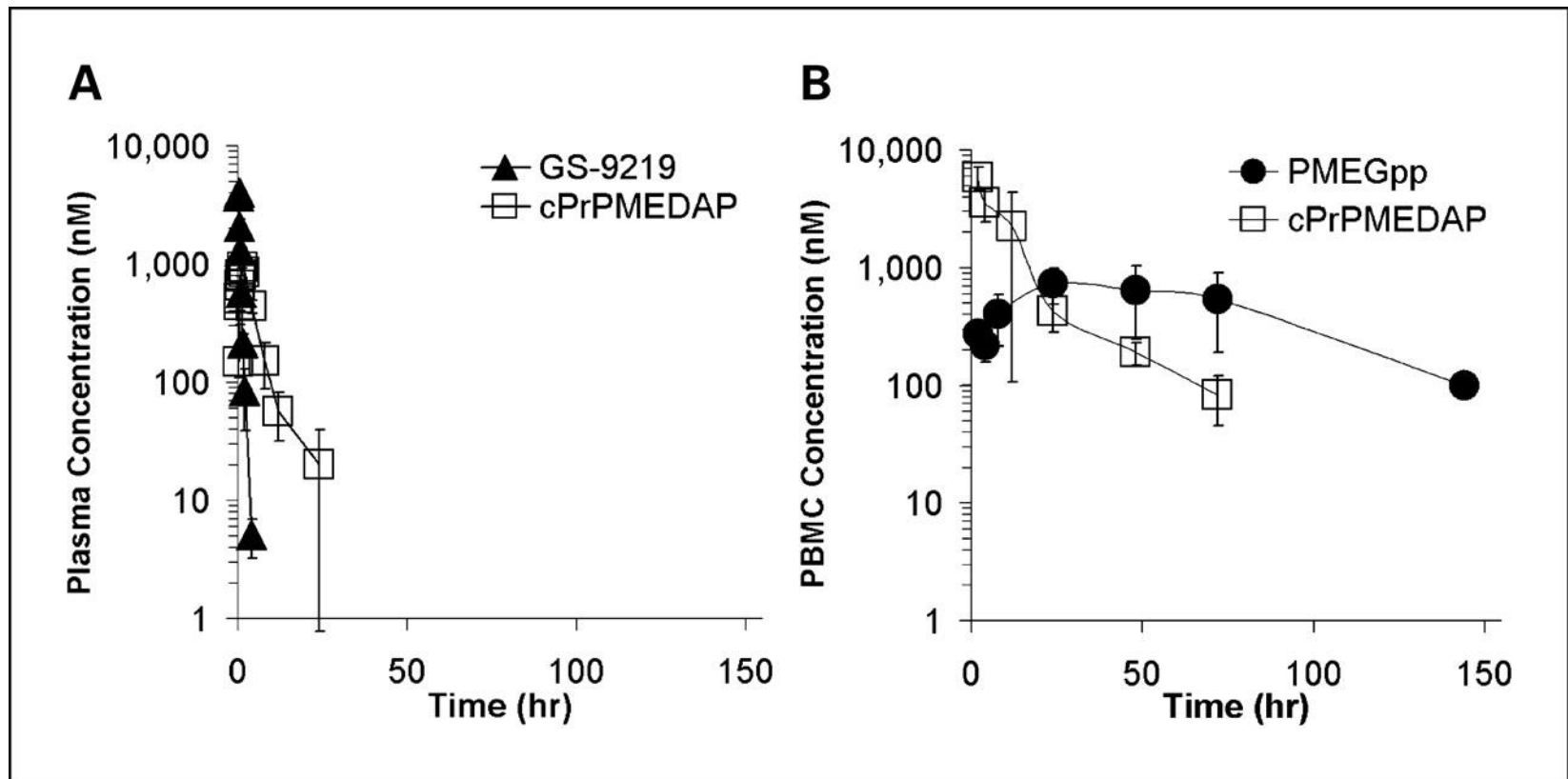
mitogen stimulated B cells

- Human 42 nM
- Canine 14 nM

- Potent inhibitor of cellular DNA polymerases α , δ and ϵ
- Efficient chain terminator of DNA synthesis resulting in -cell cycle arrest and apoptosis

Pharmacokinetics and lymphocyte loading

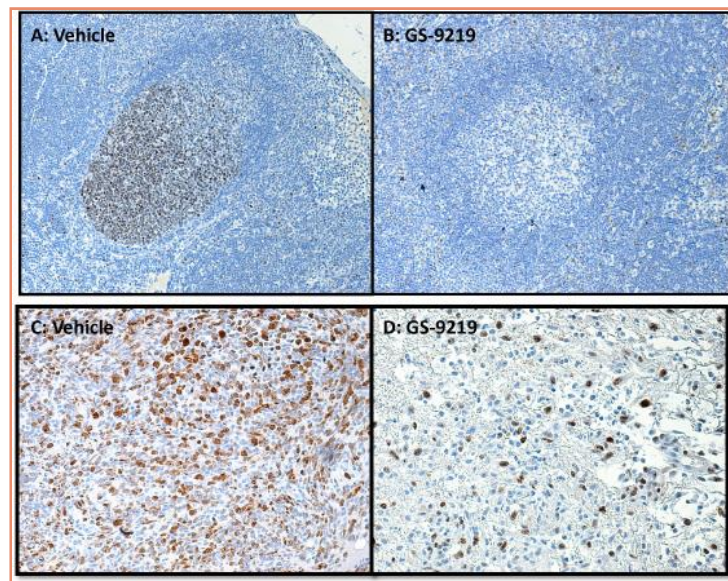
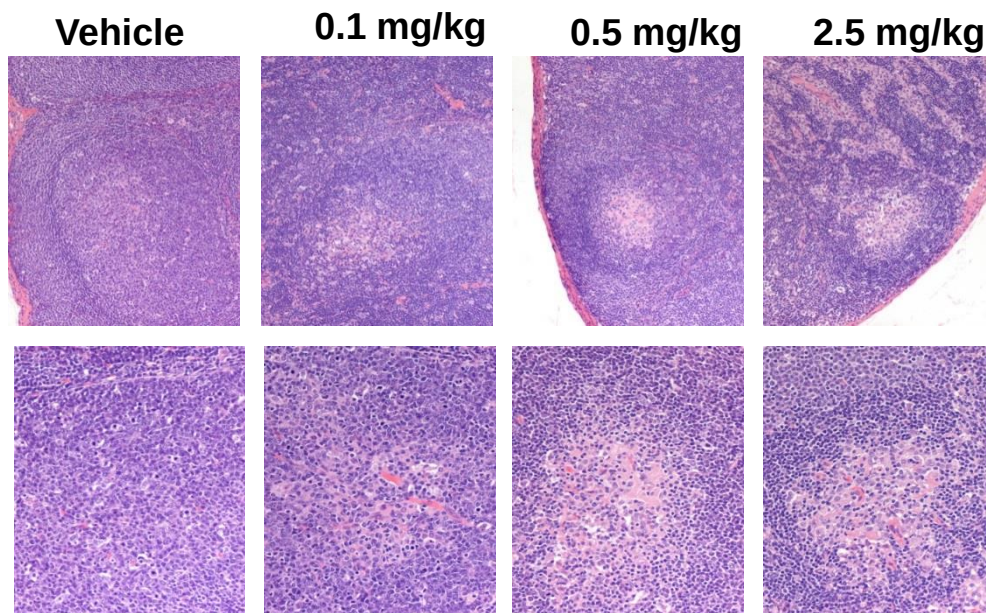
Delivery of PMEGpp to lymphoid cells GS-9219 30-min i.v. infusion of 3 mg/kg



mean of results obtained from three animals; bars, SD

Effects on lymphoid cells in vivo

**Mesenteric Lymph Nodes , 24 hours after the last dose in laboratory dogs
GS-9219 SID, IV, 5days**



Rationale for investigation in dogs with hematological cancers

- High plasma carboxyesterase levels rodents precluded their use in preclinical efficacy evaluation of GS-9219
- GS-9219 depleted germinal center B lymphocytes while sparing other tissues in laboratory dogs
- Canine NHL is a relevant model for preclinical evaluation
- Veterinary teaching hospitals have extensive experience in animal clinical studies
- Investigation in dogs with hematological cancers represented a win-win scenario - potential benefit to canine patients while establishing POC and assessment of therapeutic index.

Investigation of GS 9219 in dogs with hematological cancers

Key endpoints obtained

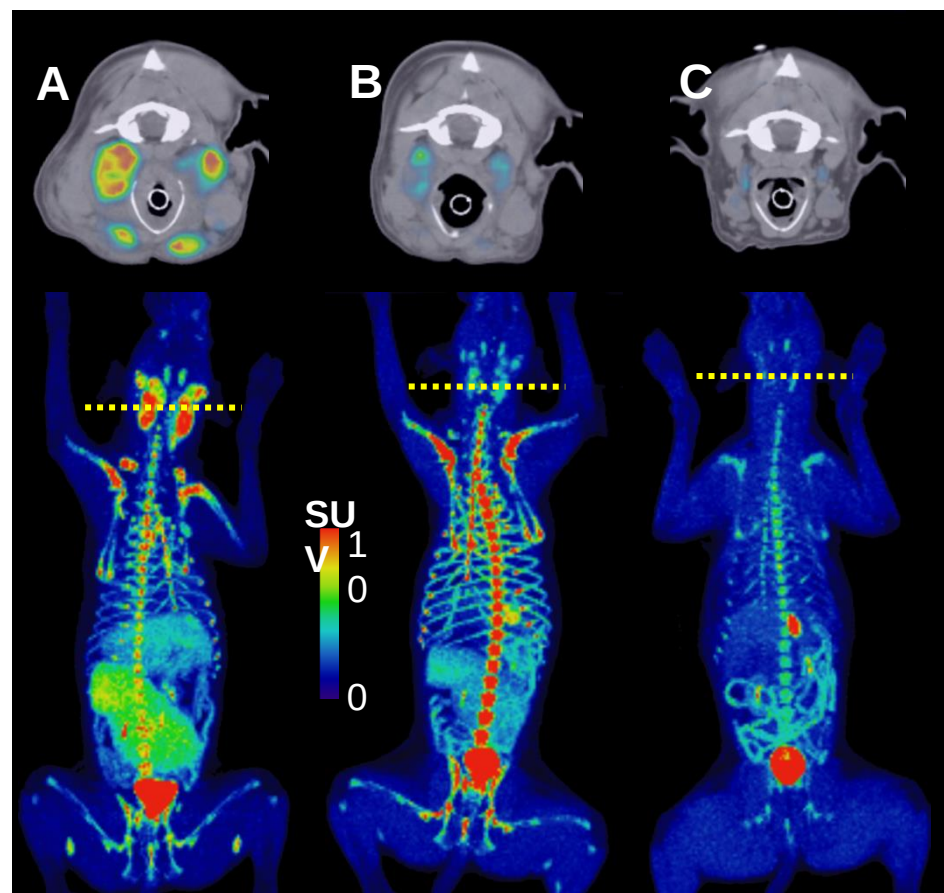
- Pharmacokinetics and “loading”
- Efficacy/activity- NHL, ALL, MM, Cutaneous lymphoma
- Evaluation of different doses, schedules, and combinations with SOC
- Evaluation of response post-relapse
- Safety assessment - intensive monitoring – acute and chronic

Responses in canine patients with NHL

- Collaboration with Drs. Vail and Thamm - School of Veterinary Medicine, University of Wisconsin-Madison & Animal Cancer Center, Colorado State University



FLT-PET/CT



Responses in canine patients with non-Hodgkin's Lymphoma

Responses in Dogs with NHL Treated with GS-9219 Monotherapy

Response Criteria	All NHL (n= 50)	B cell NHL (n = 34)	T cell NHL (n = 13)	Naïve NHL (n = 22)	Refractory or Relapsed NHL (n = 28)
CR rate	50%	71%	0%	64%	39%
PR rate	40%	26%	69%	36%	43%
Overall RR	90%	97%	69%	100%	82%
Mean PFS (days)	127 ± 157	143 ±142	37 ± 37	164 ± 172	99 ± 141
PFS range (days)	8 – 751	8 – 751	8 - 123	8 – 751	8 – 709

Results of an investigation in dogs with cancer- GS-9219

Did the paradigm enable success?

- Enabled POC in targeted diseases critical for development
 - Canine patients benefited from treatment and SOC treatment options were offered to all dogs/owners
 - Enabled long term safety evaluation and identification of adverse events which had the potential to occur in human patients
-
- Phase 1 outcome in human patients was not optimal - discontinued
 - Gilead Sciences out-licensed GS-9219 to VetDC

GS-9219 → VDC-1101 → Tanovea
(rabacfosadine)

