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

Daniel B. Tumas
Gilead Sciences, Inc
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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?

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

1. Cancers for which the outcome in dogs is predictive for humans.
3. Human cancers with high unmet need that are recapitulated in dogs.
5. High Potential for benefit - humans and/or dogs - Win-Win?
GS 9219 - anti-proliferative nucleotide analog pro-drug

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

EC50 inhibition of proliferation
mitogen stimulated B cells
- Human 42 nM
- Canine 14 nM

Clin Cancer Res 2008;14:2824-2832
Pharmacokinetics and lymphocyte loading

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

A

Plasma Concentration (nM)

GS-9219

B

PBMC Concentration (nM)

PMEGpp
cPrPMEDAP

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

Vehicle  0.1 mg/kg  0.5 mg/kg  2.5 mg/kg

A: Vehicle  B: GS-9219
C: Vehicle  D: GS-9219

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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.
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**

A. Pretreatment; B. 5 Days After a Single 0.66 mg/kg Dose of GS-9219; C. 3 Weeks after completion of 5 cycles
Responses in Dogs with NHL Treated with GS-9219 Monotherapy

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

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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