IOM Workshop on Comparative Oncology
Pharmacokinetics in Companion Animal Cancer Studies

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Topics to be Covered

1. Carrying out PK studies in companion animals
   a. Variability in PK data
   b. Utilization of PK data
2. Dose finding studies inform PK and toxicity (PD)
   a. Dose escalation studies
   b. Drug delivery and toxicity assessment in a manner consistent with human use
3. Impact of tissue sampling on PK/PD measures
   a. PK/PD correlations
   b. Assessment of clinical applicability
Carrying Out PK Studies

- Time course sampling in individual animals
- Drug dispensing done in a manner consistent with human medicine
- Sample collection done by a professional staff
- Defined SOPs for sample processing
Variability in Pharmacokinetics

Doxorubicin in Humans and Dogs

Exposure following a therapeutic dose of 60 mg/m² (humans) or 30 mg/m² (dogs)

<table>
<thead>
<tr>
<th>Species</th>
<th>AUC (ng/ml) x hr</th>
<th>SD</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human (n=12)</td>
<td>1536</td>
<td>422</td>
<td>27.5%</td>
</tr>
<tr>
<td>Dog (n=20)</td>
<td>1591</td>
<td>327</td>
<td>20.5%</td>
</tr>
</tbody>
</table>

- Similar drug exposure at the MTD-based dose
- Similar variability is observed
- Time-course of drug exposure is similar
Variability in Pharmacokinetics

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Human(^1) (50 mg qD)</th>
<th>Dog(^2) (3.25 mg/kg EOD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}}) (ng/ml)</td>
<td>27.7 (51%)</td>
<td>79.0 (32%)</td>
</tr>
<tr>
<td>(C_{\text{min}}) (ng/ml)</td>
<td>44.0 (59%)</td>
<td>19.1 (62%)</td>
</tr>
<tr>
<td>AUC(_{0-t}) (ng/ml) x hr</td>
<td>420 (50%)</td>
<td>1870 (35%)</td>
</tr>
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For Dose Comparison:
Human 50 mg is approximately = 30 mg/m\(^2\) or 0.7 mg/kg

Dog 3.25 mg/kg is approximately = 100 mg/m\(^2\)
Utilization of PK Data
(Microdosing and TDM)

Microdosing with dasatinib to determine daily dose to achieve a $C_{\text{max}}$ of 35 nM, a putative active plasma concentration of drug.

Predicted drug levels at 0.65 mg/kg dasatinib dose

- Test efficacy and toxicity at target dose
- Determine feasibility and accuracy of PK-directed, microdosing-based therapeutic drug monitoring

Current ongoing study, PI: Dr. Seguin
Dose Escalation Studies
(Dog Phase I Trials)

- Dose escalation PK and Tox performed
- Exposure parameters defined in plasma and PBMCs for parent and active metabolites
- More optimal schedules defined in terms of efficacy and toxicity
Drug Delivery and Toxicity Assessment

Infusion vs. Bolus Delivery

For companion animal trials, drug is delivered in an appropriate vehicle using drug delivery schemas consistent with what is done in human trials.
Toxicity Assessment
Graded and Standardized

- Sunitinib in humans
  - Similar:
    - Weakness
    - Vomiting
    - Neutropenia
  - Species Dependent:
    - Diarrhea
    - Hypertension
    - Skin toxicity

- Toceranib in dogs
  - Similar toxicities observed as well as some that were more species dependent:

Tissue Sampling
PK/PD Correlations

Plasma and tumor drug levels of hydroxychloroquine (HCQ) and the primary active metabolite N-desethylyHCQ (DHCQ) for the inhibition of autophagy.

- HCQ and DHCQ accumulate approximately 100-fold in tumor tissue as compared to plasma levels.
- There is no correlation between plasma and tumor drug levels.

Thus, using plasma drug levels as a measure of drug exposure for potential dose modification is not indicated by these findings.

PBMCs from dogs treated with HCQ showed changes consistent with inhibition of autophagy by HCQ.

- Increase in LC3 positive cells
- Increase in autophagic vesicles as measured by EM

No correlation between autophagy inhibition in PBMCs and tumors

Barnard et al. *Autophagy* 10:1415, 2014
Clinical Trials of HCQ in Cancer

**Combined autophagy and HDAC inhibition**
A phase I safety, tolerability, pharmacokinetic, and pharmacodynamic analysis of hydroxychloroquine in combination with the HDAC inhibitor vorinostat in patients with advanced solid tumors

Devangini Mahalingam,1,2 Monica Mia,1 John Sarantopoulos,1 Leslie Wood,1 Ravi Amaravadi,1 Lisa Davis,1 Alain Mita,2 Tyler J Currie,1 Claudia M Espitia,1 Steffan T Nawrocki,1 Francis J Giles,1 and Jennifer S Carew1,2

**Combined MTOR and autophagy inhibition**
Phase I trial of hydroxychloroquine and temsirolimus in patients with advanced solid tumors and melanoma

Reshma Rangwala,1,3 Yunyoung C Chang,1,4 Janice Hsu,1 Kenneth Algazy,1 Tracey Evans,1 Leslie Fecher,1,3 Lynn Schuchter,1 Drew A Torgian,1,3 Jeffrey Piasco,2,3 Andrea Troxel,1 Kay-See Tan,1 Daniel F Heitjan,2 Angela Demichele,2 David Vaughn,2 Maryann Redlinis,2 Abass Abazi,2 Jonathon Kaiser,2 Laura Pontiggia,2 Lisa E Davis,1 Peter J O'Dwyer,2,5 and Ravi K Amaravadi6,7

**Phase I trial of hydroxychloroquine with dose-intense temozolomide in patients with advanced solid tumors and melanoma**

Reshma Rangwala,1,3 Robert Leone,1,3 Yunyoung C Chang,1,4 Leslie Fecher,1,3 Lynn M Schuchter,1 Amy Kramer,1 Kay-See Tan,2 Daniel F Heitjan,2 Glenda Rodgers,1 Maryann Gallagher,1 Shengfu Piao,1 Andrea B Troxel,1 Tracey Evans,1 Angela DeMichele,2 Katherine L Nathanson,1 Peter J O'Dwyer,2 Jonathon Kaiser,2 Laura Pontiggia,2 Lisa E Davis,1,3,4 and Ravi K Amaravadi6,7

**A phase I/II trial of hydroxychloroquine in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme**

Myrna R Rosenfeld,1,3 Xiaobo Ye,1,3 Jeffrey G Supko,1,3 Serena Desideri,1,3 Stuart A Grossman,1,3 Steven Brem,1,3 Tom Mikkelson,1,3 Daniel Wang,1 Yunyoung C Chang,1,4 Janice Hsu,1 Quentin McAfee,1,3 Joy Fisher,1,3 Andrea Troxel,1 Shengfu Piao,1 Daniel F Heitjan,2 Kay See Tan,1 Laura Pontiggia,2 Peter J O'Dwyer,2,5 Lisa E Davis,1,3 Ravi K Amaravadi6,7

**Combined autophagy and proteasome inhibition**
A phase 1 trial of hydroxychloroquine and bortezomib in patients with relapsed/refractory myeloma

Den T Vogl,1,3 Edward A Stadtmauer,1 Kay See Tan,2 Daniel F Heitjan,2 Lisa E Davis,1 Laura Pontiggia,2 Shengfu Piao,1 Yunyoung C Chang,1,4 Emma C Scott,1 Thomas M Paul,1 Charles W Nichols,1 David L Porter,1 Janeen Kaplan,1 Gayle Malloy,1 James E Bradner,1 and Ravi K Amaravadi6,7

**Phase I clinical trial and pharmacodynamic evaluation of combination hydroxychloroquine and doxorubicin treatment in pet dogs treated for spontaneously occurring lymphoma**

Rebecca A Barnard,1 Luke A Wittenburg,1 Ravi K Amaravadi1, Daniel L Gustafson,1 Andrew Thorburn,3 and Douglas H Thamm1,3

Canine trial published as part of a series with human clinical trials of HCQ