Comparative Clinical Trials: Designs with companion animal and Caregiver in mind

David M. Vail, DVM, Diplomate ACVIM (Oncology)
Professor and Barbara A. Suran Chair in Comparative Oncology
The Evolution of the Pet Dog in Our Lives
The Evolution of the Pet Dog in Our Lives

Julia Stephanus
Client Enthusiasm for Investigational Trials

- Highly motivated
  - Web surfing
  - Media coverage
- No standard of care
- Financial incentive
  - “win – win?”
- ‘Altruism’
- Compliance is excellent
  - e.g., 80% necropsy
<table>
<thead>
<tr>
<th>Trial</th>
<th>Aim</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I clinical trials</td>
<td>Dose finding</td>
<td>• Toxicity and dose-limiting toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pharmacokinetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maximum tolerated dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pharmacodynamics/biomarkers</td>
</tr>
<tr>
<td>Phase II clinical trials</td>
<td>Anti-tumour activity</td>
<td>• Response rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Toxicity</td>
</tr>
<tr>
<td>Phase III clinical trials</td>
<td>Clinically important activity</td>
<td>• Progression-free interval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cost–benefit analysis</td>
</tr>
</tbody>
</table>

Figure 1 | Structure of phase I, II and III clinical trials.
Who enters phase I

- Refractory to standard-of-care
- Often heavily pretreated and poor performance scores

In veterinary trials, who enters a phase I?
- No standard-of-care exists
- Standard-of-care inadequate
- Financial constraints of standard-of-care
  - Offset treatment costs
  - Additional incentive for alternate therapy at failure
- Altruistic?
Phase I Trial = Companion/Client Concerns

**Goal:** determine the MTD

**Concerns:**
- Deny standard of care
- Efficacy low especially early cohorts
- Toxicity: unknown and likely in later cohorts
- Starting dose and escalation method

**Methods to relieve concerns:**
- Educational Consent
- < # treated at low dose cohorts
  - Client advocacy as to cohort
  - Accelerated titration
  - Within cohort escalation
  - PK/Target modulation Strategies
  - BOD
  - Normal dog data
- Allow sufficient time for AEs to occur
- Cover cost of managing adverse events
Phase I Oncology Studies: Evidence That in the Era of Targeted Therapies Patients on Lower Doses Do Not Fare Worse

Rajul K. Jain¹, J. Jack Lee³, David Hong¹, Maurie Markman², Jing Gong¹, Aung Naing¹, Jennifer Wheler¹, and Razelle Kurzrock¹

![Graph showing estimated probability of no disease progression or death over time since starting study treatment. The graph includes Kaplan-Meier curves for different dose groups: Low-Dose (n=170), Medium-Dose (n=200), High-Dose Exclude Over MTD (n=218), and High-Dose Include Over MTD (n=313). The p-values for differences between groups are 0.21 for excluding patients over MTD and 0.13 for including patients over MTD.](image-url)
Phase II
= “Efficacy trial”

Goal: characterize clinical/biologic activity (i.e., which tumor types or targets respond)

Concerns:
- Deny standard of care
- Toxicity: Chronic and low incidence AEs still unknown
- Larger numbers required
- Surrogate endpoints

Methods to relieve concerns:
- Educational consent
- 3 R’s
- Phase I/II combinations
- 2-stage min/max design
- ‘Pick-the-winner’ trials (relaxed power)
- Continuous learning/adaptive designs
- Enrichment
- Cover cost of managing adverse events

Clin Cancer Res 2009; 15(6) – CCR Focus section
3 indenoisoquinolines (topoisomerase 1 Inhibitors) Pick the winner Phase I/II
Enrichment

- Intent is to select a subset of patients to enroll that are relatively homogenous with respect to *predictive* factors and randomize only these patients likely to respond or benefit

- e.g:
  - “drugable” target identification
  - Exclude poor prognostic group
Enrichment example:

- Trastuzumab *Her-2* mAb + chemo
- 469 patients needed in study when entering only *Her-2* over-expressers (1 yr. OS 78% vs. 67%)
- If unselected patients - 23,586 would have been required to show the difference!
- Problem: what if your wrong about the “target” (off-target effects)?

Slamon DJ, et al. NEJM 2001;344.
Phase III trials (Comparative)

Goals:
- Effect of treatment vs natural history of the disease
- Is new treatment better than standard treatment
- If new Tx = old Tx, is it less toxic or less expensive

Concerns:
- Use of placebo?
- Deny standard of care
- Larger numbers required

Methods to relieve concerns:
- Consent
- Placebo = Best Supportive Care
- early tripwire/stopping rules
- Trial designs
  - Continuous learning/adaptive designs
  - Multi-arm trials (shared control group)
  - Unequal randomization
  - Randomized discontinuation
  - Cross-over trials
Bayesian (continuous learning) Designs

- **Frequentist approach**
  - Traditional method uses fixed parameters - inflexible
  - e.g., Initial assumptions about RR or OS cannot change

- **Bayesian** - makes statistical inferences using:
  - Accumulated data
  - Historical data
  - Data from other trials

- **Adaptive designs**:
  - Can stop trials early
  - Can change randomization weight to better performing arms
  - Can add new arms
  - Extend accrual beyond target
Bayesian Example

- EGFR2 +ve breast cancer study
- Initial design = 164 patients
- Bayesian approach after 34 patients enrolled
  - 67% CR in study arm
  - 25% in control
  - Bayesian predictive probability of 95% if 164 enrolled so trial stopped and Phase III initiated early

Figure 3: Randomization probabilities for randomization a patient into the toceranib arm for patients with biomarker status “c-KIT+/KIT loc+”. This suggests that if mut+/loc+ dogs have an improved response with toceranib in the run-in phase, these dogs may have a 60-80% chance of bring randomized to this arm subsequently, increasing the chance of benefit to the patient.
Stopping Rules

- Terminate trial within a predetermined adaptive trial design
- Protect patients from unsafe drugs and/or hasten availability of superior drugs
- 3 reasons to stop:
  1. Investigational drug clearly better than control
  2. It is clearly worse than control (< activity, > toxicity)
  3. It is not likely to be better = “stopping for futility”
Randomized Discontinuation

1. Treat all patients initially on the experimental regimen for a defined period of time.

2. Randomize only those that remain stable (patients who progress are taken off study and patients who respond continue to receive the experimental regimen).

3. Compare placebo vs. experimental regimen from time of randomization.
Phase 0 Trials

- “exploratory IND”
- Proof of principle
  - target modulation
  - Sub-therapeutic dose
  - Assay development and SOPs
  - Short (7 days)
  - Ethical questions
  - Choose which compounds to move forward to Phase I


Clin Cancer Res 2008; 14(12) – CCR Focus section
Phase 0 Example

• Does drug buildup in tumor histology of interest
• Is target modulated in tumor histology of interest
  – Includes conversion of prodrug
• Client incentive?
Consolidated Standards of Reporting Trials
CONSORT Statement 2010 Flow Diagram

Assessed for eligibility (n= )
- Excluded (n= )
  - Not meeting inclusion criteria (n= )
  - Declined to participate (n= )
  - Other reasons (n= )

Randomized (n= )

Allocated to intervention (n= )
- Received allocated intervention (n= )
- Did not receive allocated intervention (give reasons) (n= )

Lost to follow-up (give reasons) (n= )
Discontinued intervention (give reasons) (n= )

Analysed (n= )
- Excluded from analysis (give reasons) (n= )

Allocated to intervention (n= )
- Received allocated intervention (n= )
- Did not receive allocated intervention (give reasons) (n= )

Lost to follow-up (give reasons) (n= )
Discontinued intervention (give reasons) (n= )

Analysed (n= )
- Excluded from analysis (give reasons) (n= )


For more information, visit [www.consort-statement.org](http://www.consort-statement.org).
Methods to Enhance Bidirectional Flow

- Preclinical models:
  - Small animal
  - Beagle dog
  - Non-human primate

- Phase I human clinical trials
- Phase II human clinical trials
- Phase III human clinical trials

- Tumour-bearing dog studies:
  - Activity
  - Toxicity
  - Pharmacokinetics
  - Pharmacodynamics

- Tumour-bearing dog studies:
  - Dose
  - Regimen
  - Schedule
  - Biomarkers
  - Responding histologies
  - Combination therapies

New cancer drug
Acknowledgements

Ethics, Conduct and Oversight of Clinical Trials in Companion Animals with Cancer: Report of a Workshop on Best Practice Recommendations.

Rodney Page¹, *, Phillipe Baneux², David Vail³, Lily Duda⁴, Amy LeBlanc⁵, Patricia Olson⁶, Lida Anestidou⁷, Noel Dybdahl⁸, Gail Golab⁹, Whitney Miller⁹, Christina Mazcko⁵, Wendy Shelton¹⁰, Michael Salgaller¹⁰, Christine Hardy¹.