

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



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Advancing animal and human health with science and compassion



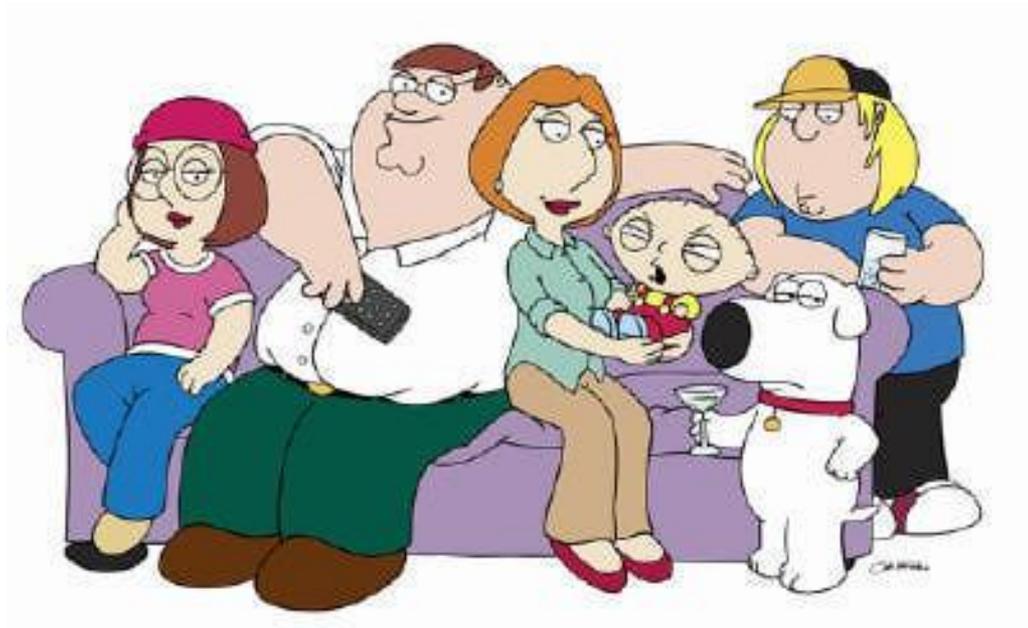
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The Evolution of the Pet Dog in Our Lives



The Evolution of the Pet Dog in Our Lives



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



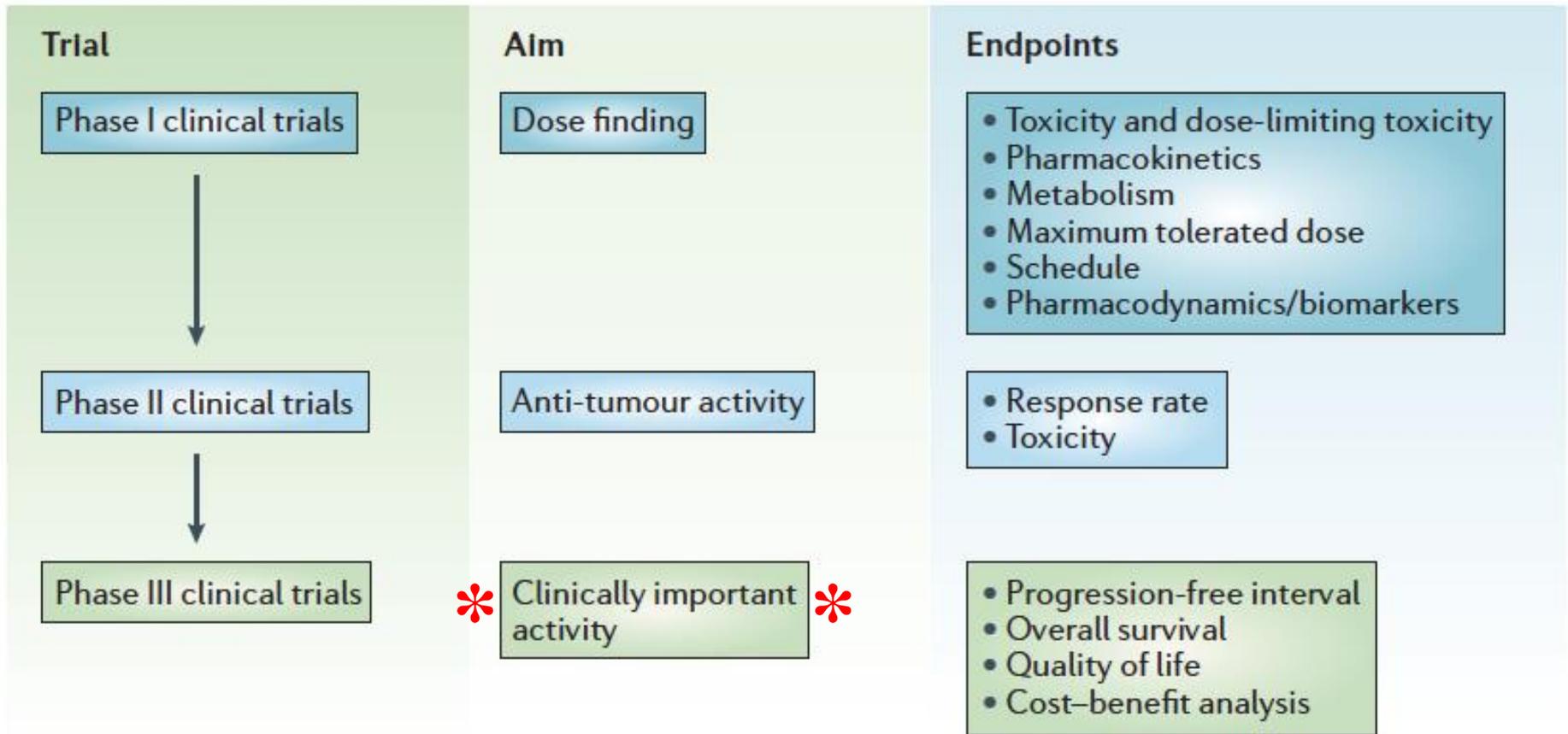


Figure 1 | Structure of phase I, II and III clinical trials.

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:

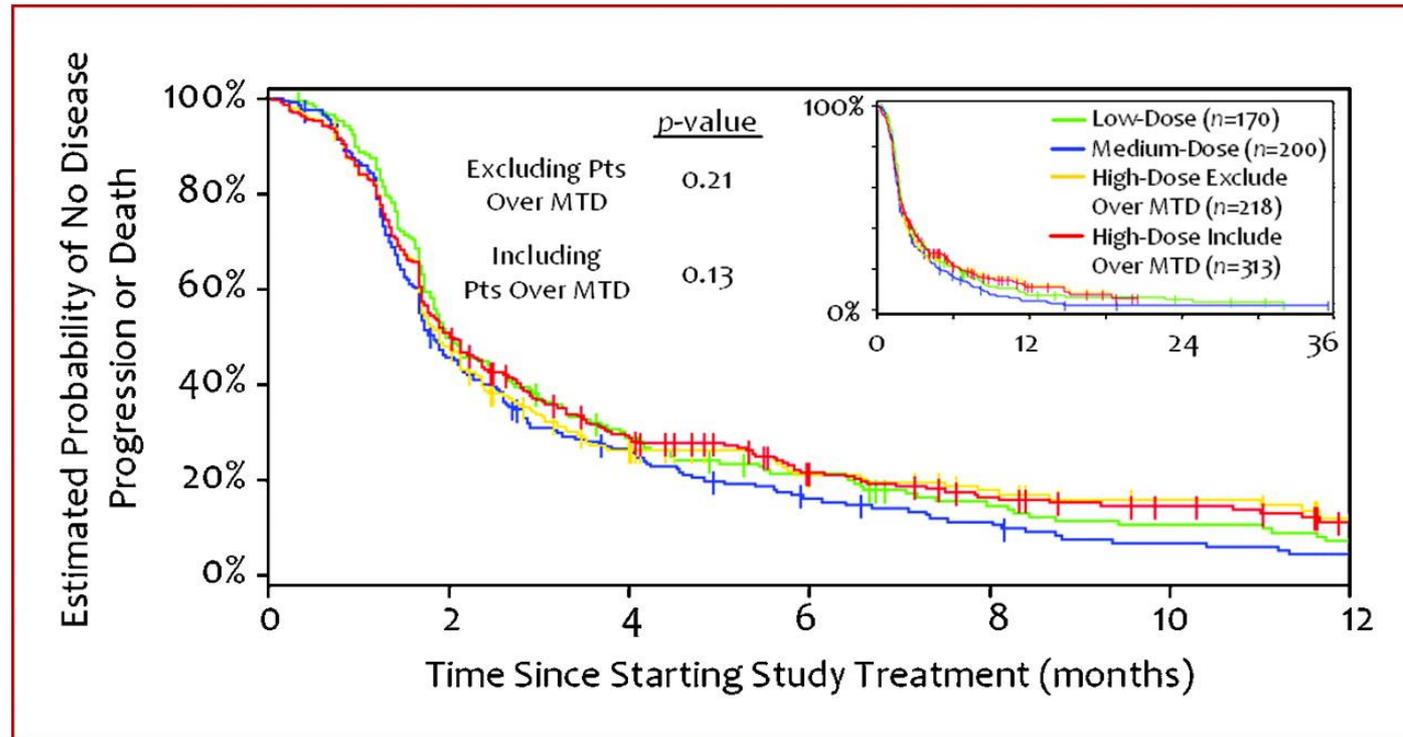
- Educational Consent
- < # treated at low dose cohorts
 - Client advocacy as to cohort
 - Accelerated titration
 - Within cohort escalation
 - PK/Target modulation Strategies
 - BOD
 - Normal dog data
- Allow sufficient time for AEs to occur
- Cover cost of managing adverse events



Cancer Therapy: Clinical

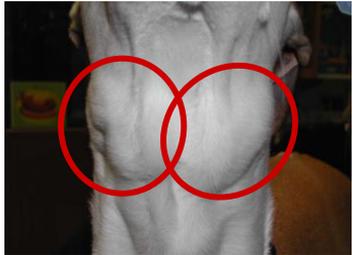
Phase I Oncology Studies: Evidence That in the Era of Targeted Therapies Patients on Lower Doses Do Not Fare Worse

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



Phase II = “Efficacy trial”

Pre-treatment Day 6 post



Clin Cancer Res 2009;
15(6) –
CCR Focus section

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

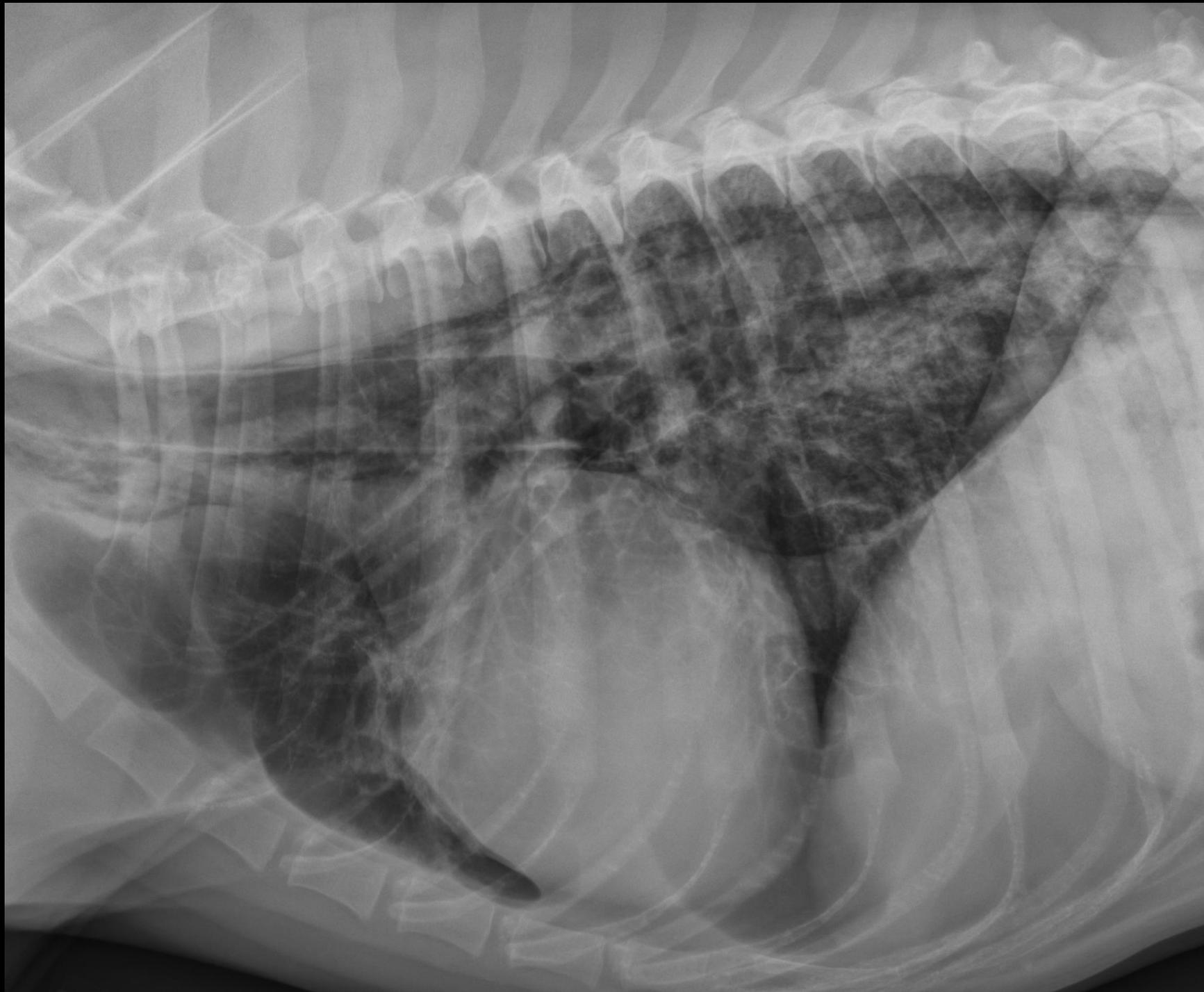


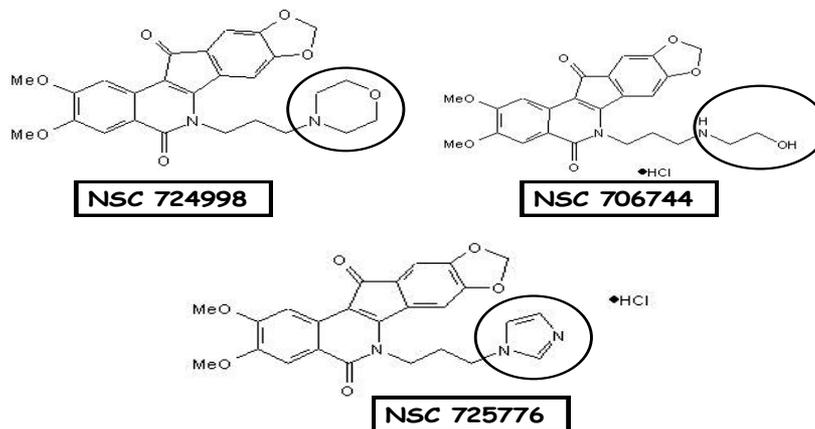
Table 1. GS-9219 scheduled treatment regimens evaluated

Cohort	GS-9219 dose (mg/kg)*	Frequency†	Dogs treated	Dose-limiting adverse events	Best response observed
Cohort 1-low	0.20	Daily for 5 d, every 21 d	7 [‡]	1	5 CR/2 PR
Cohort 1-high	0.29	Daily for 5 d, every 21 d	6 [§]	3	5 CR/1 PR
Cohort 2-low	0.66	Once every 7 d	3	0	2 CR/0 PR
Cohort 2-high	0.82	Once every 7 d	6 [§]	2	3 CR/2 PR
Cohort 3-low	0.66	Once every 14 d	3	0	1 CR/0 PR
Cohort 3-high	0.82	Once every 14 d	6 [§]	1	3 CR/2 PR
Cohort 4-low	0.66	Once every 21 d	3	0	2 CR/0 PR
Cohort 4-high	0.82	Once every 21 d	4	0	2 CR/0 PR

Clin Cancer Res 2009;15(10) May 15, 2009

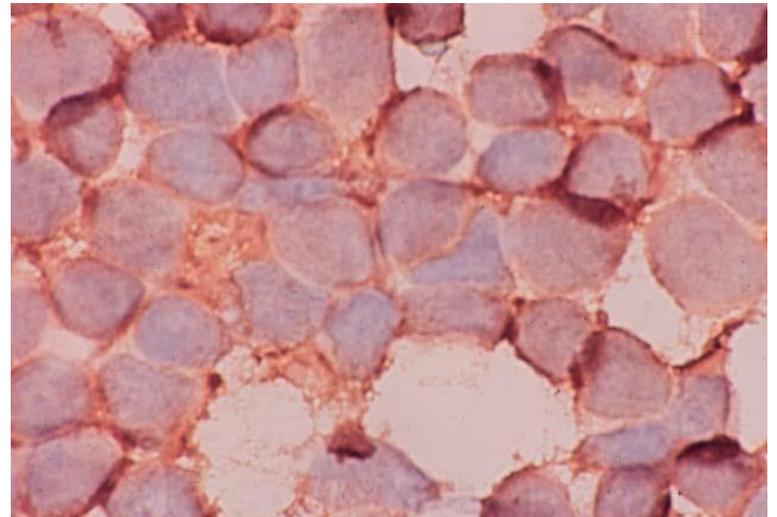
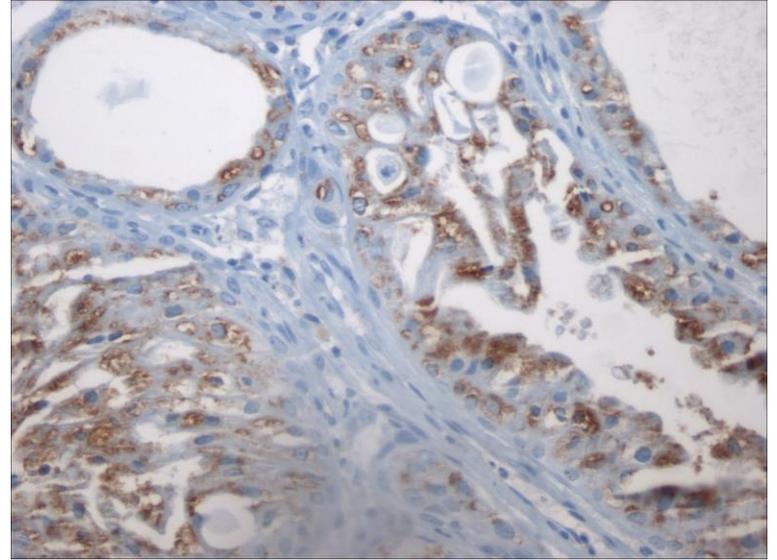
3 indenoisoquinolines (topoisomerase 1 Inhibitors) Pick the winner Phase I/II

COTC007



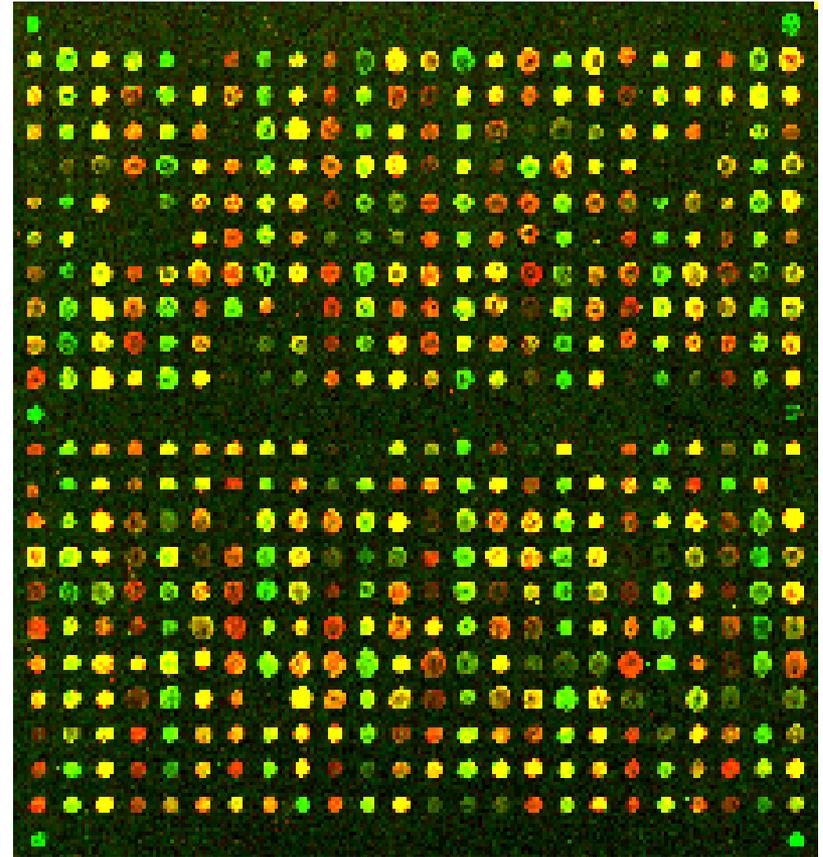
Enrichment

- 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

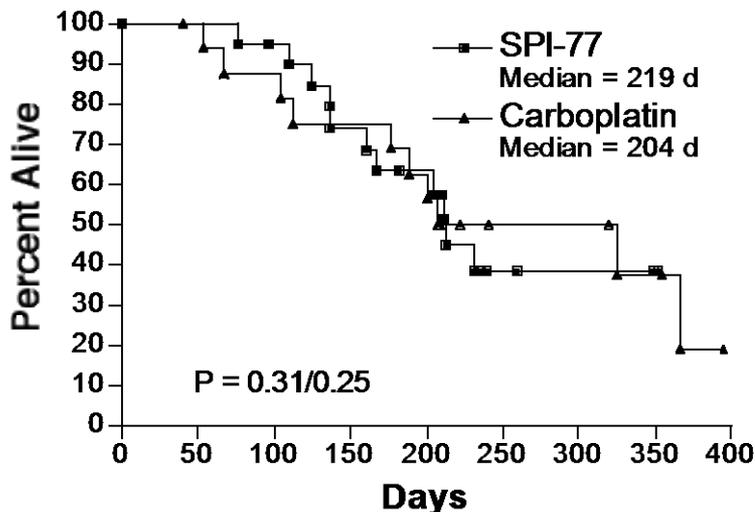
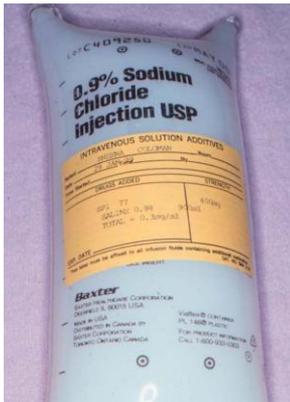


Enrichment example:

- 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)?



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

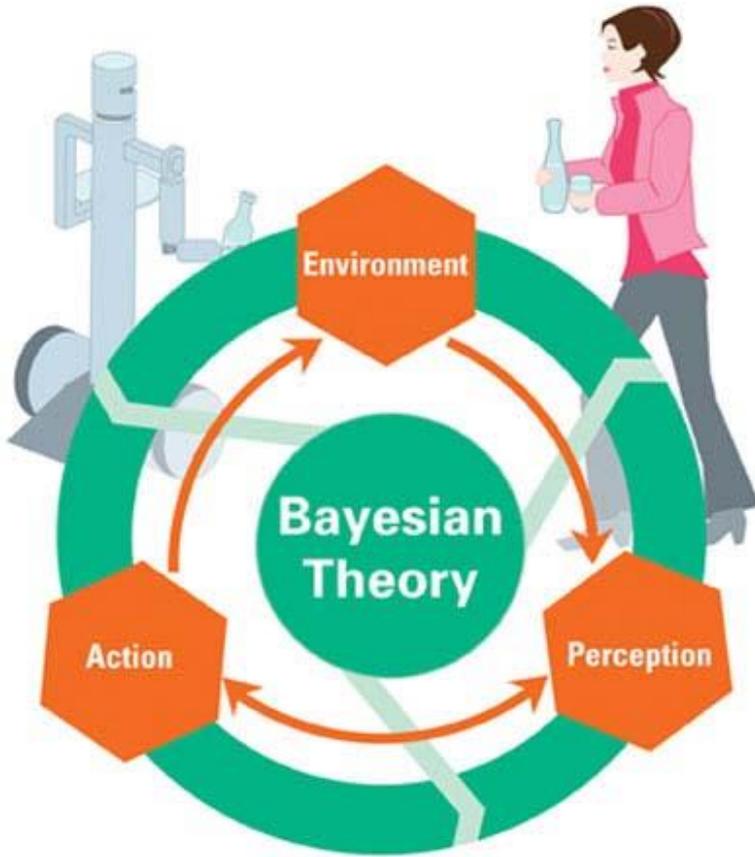
Concerns:

- 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

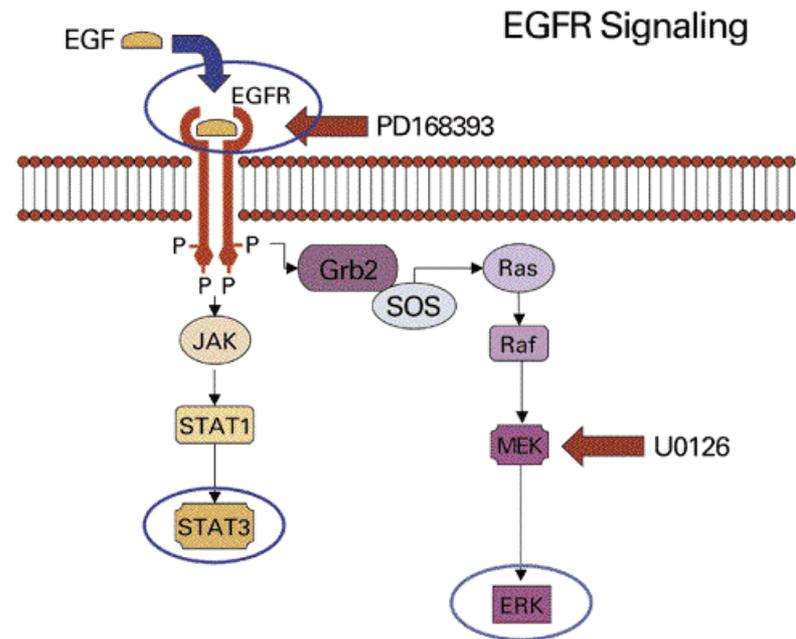
Bayesian (continuous learning) Designs



- *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



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

- D.H. Thamm, A.M. Avery, E.J. Ehrhart, J. Eickhoff, C.A. London, D.M. Vail, R.B. Rebhun, C. Clifford, K.Y. Kow

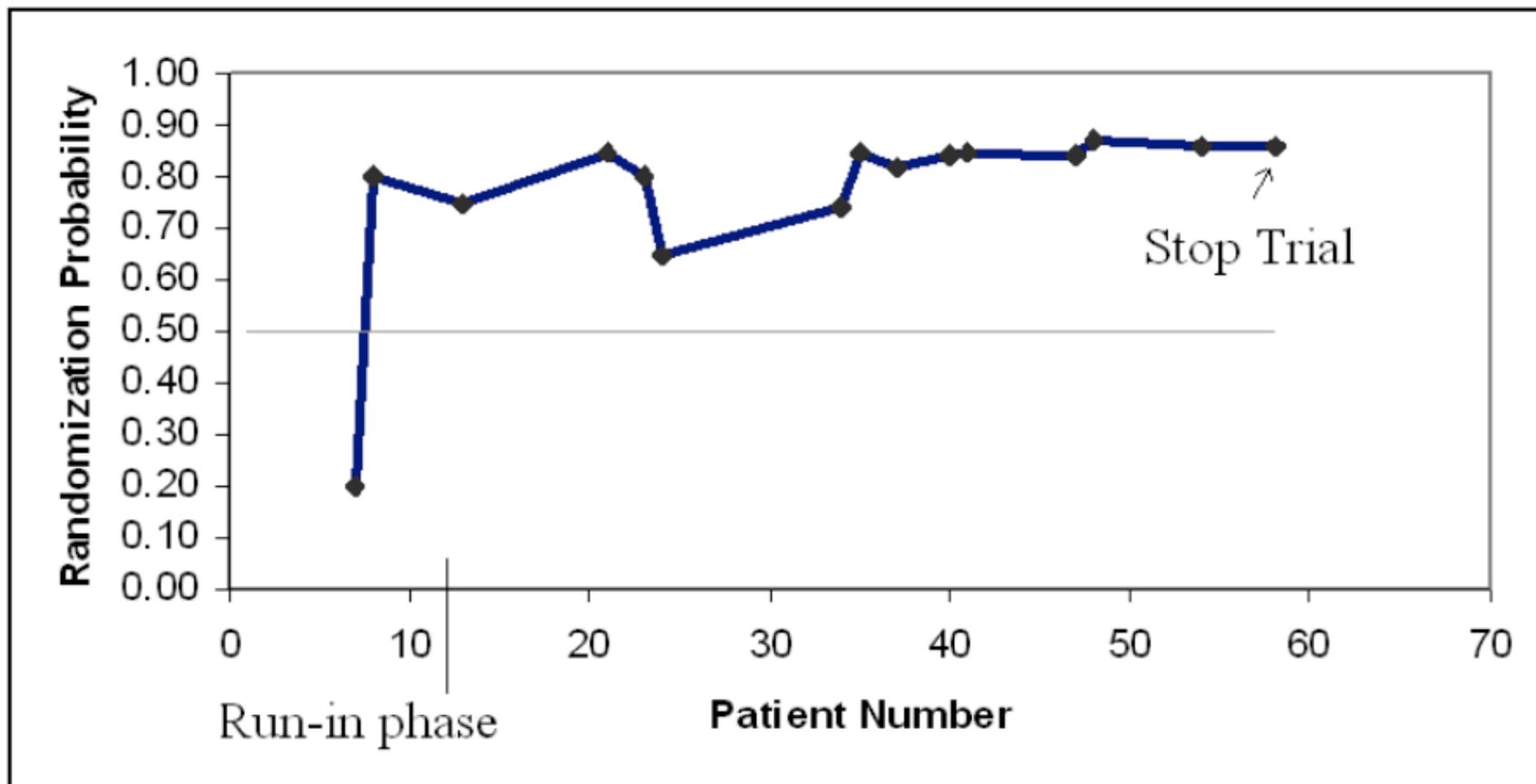


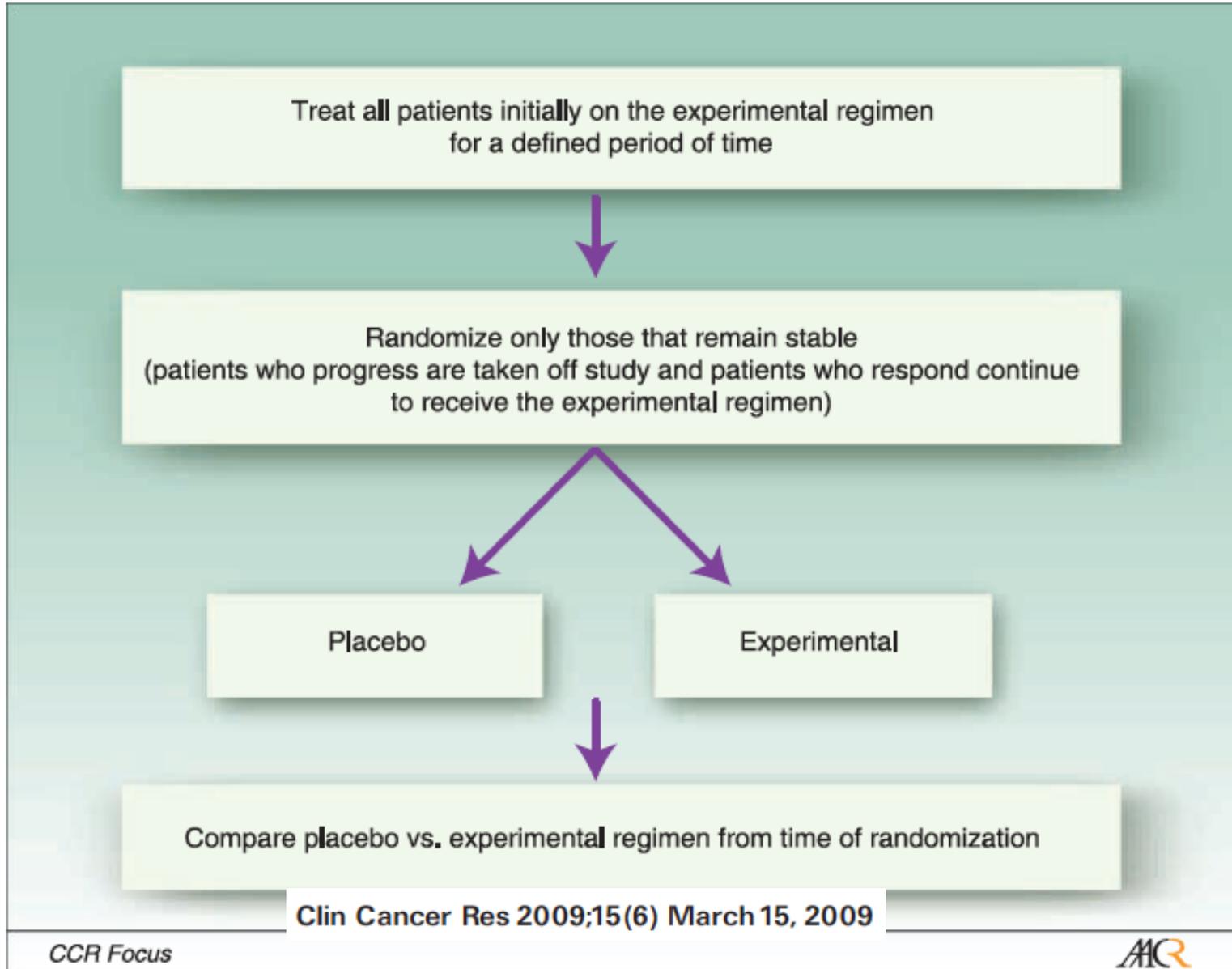
Figure 3: Randomization probabilities for randomization a patient into the toceranib arm for patients with biomarker status "c-KIT+/KIT loc+". This suggests that if mut+/loc+ dogs have an improved response with toceranib in the run-in phase, these dogs may have a 60-80% chance of being randomized to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

Stopping Rules



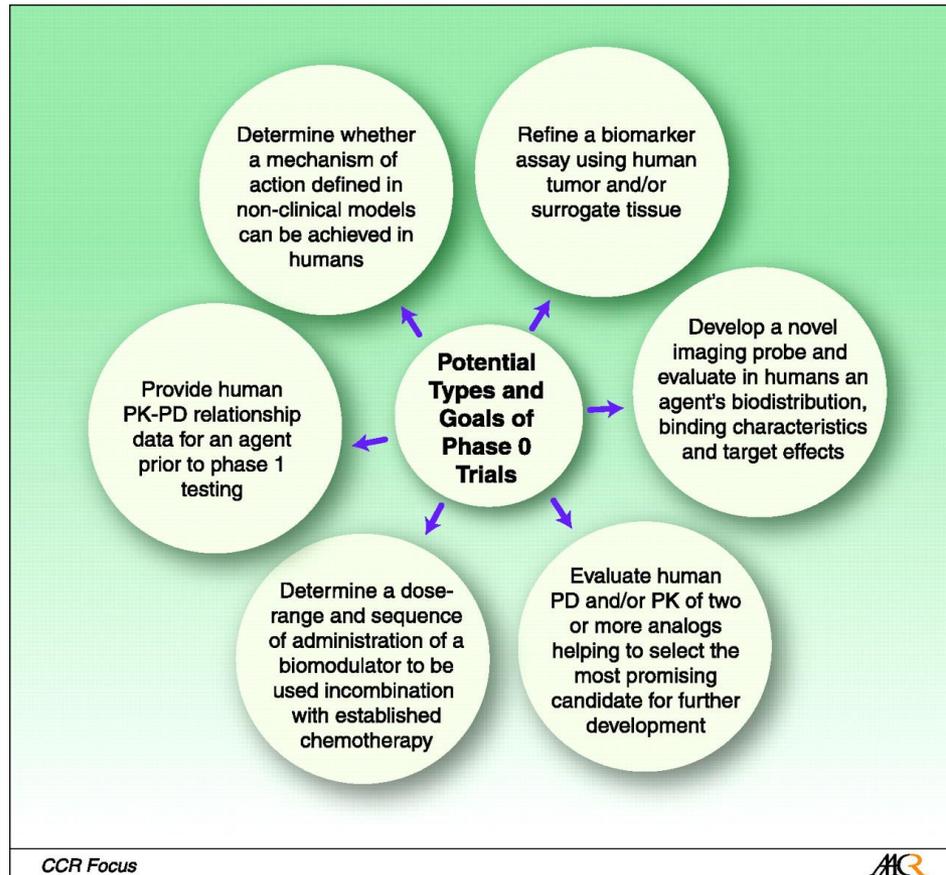
- Terminate trial within a predetermined adaptive trial design
- Protect patients from unsafe drugs and/or hasten availability of superior drugs
- 3 reasons to stop:
 1. Investigational drug clearly better than control
 2. It is clearly worse than control (< activity, > toxicity)
 3. It is not likely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

Randomized Discontinuation



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

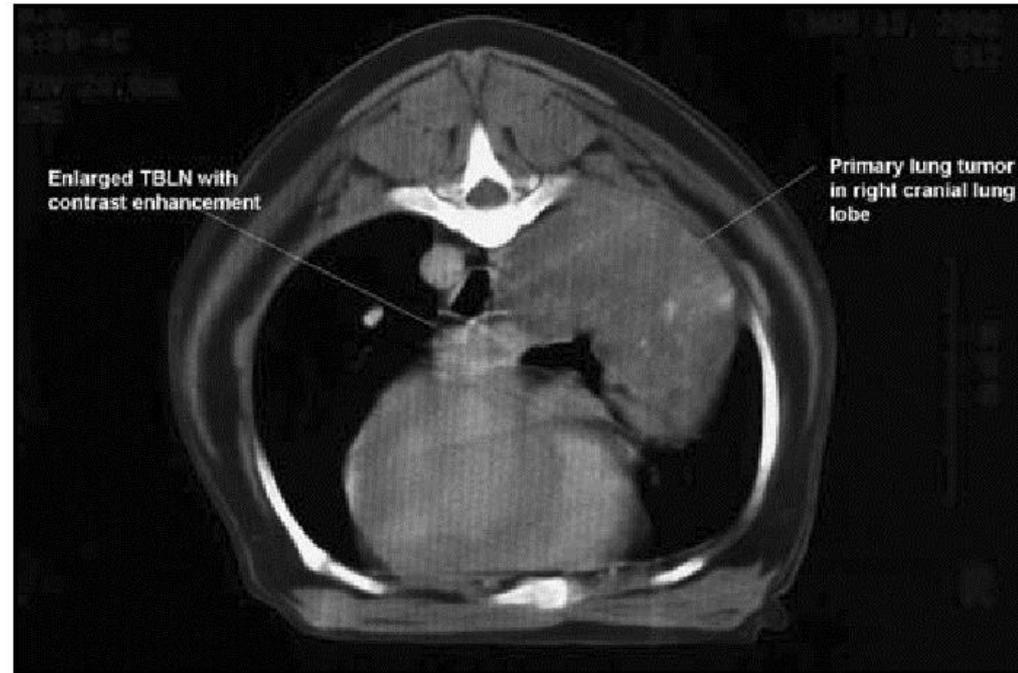


Murgo, A. J. et al. Clin Cancer Res 2008;14:3675-3682

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?

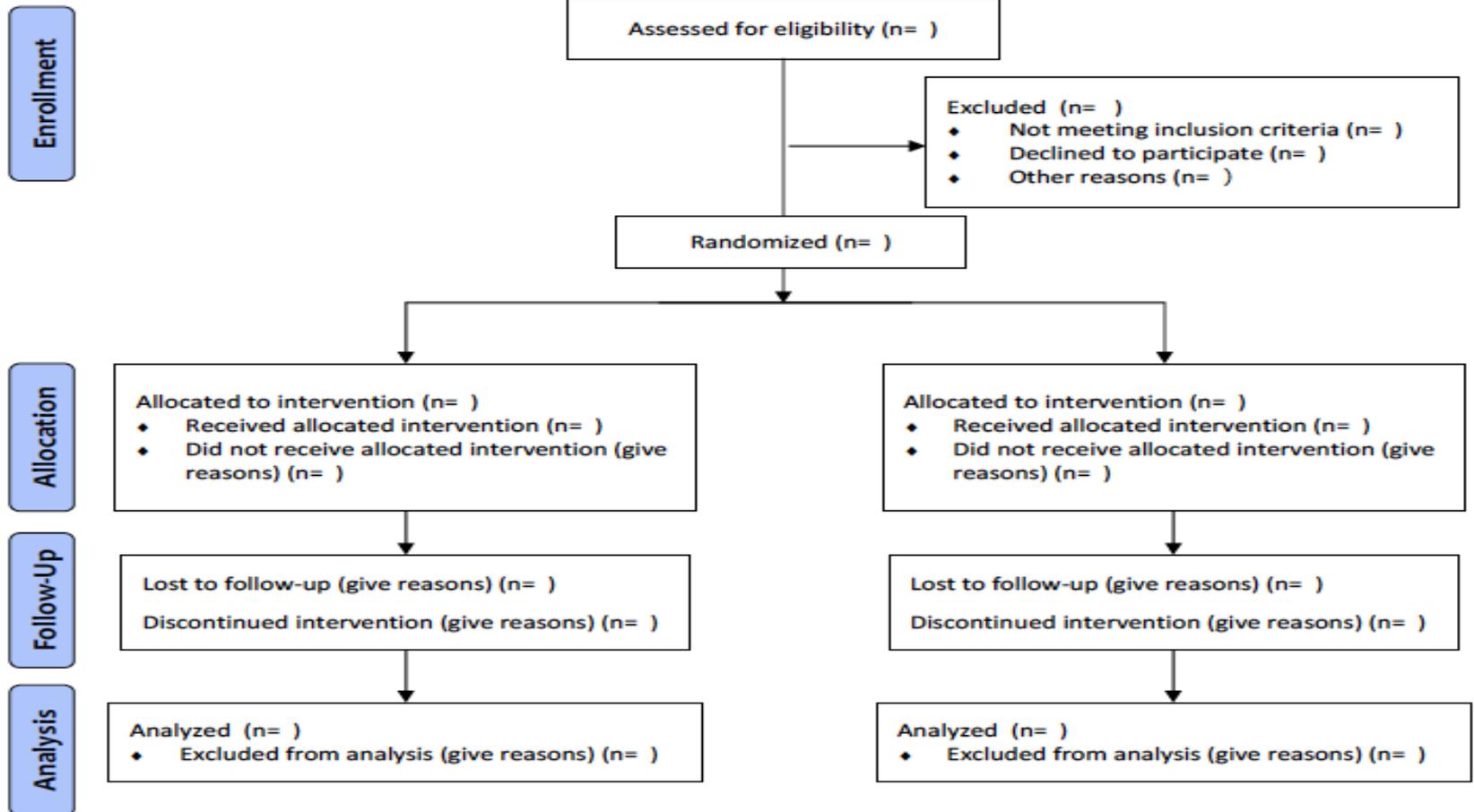




Consolidated Standards of Reporting Trials



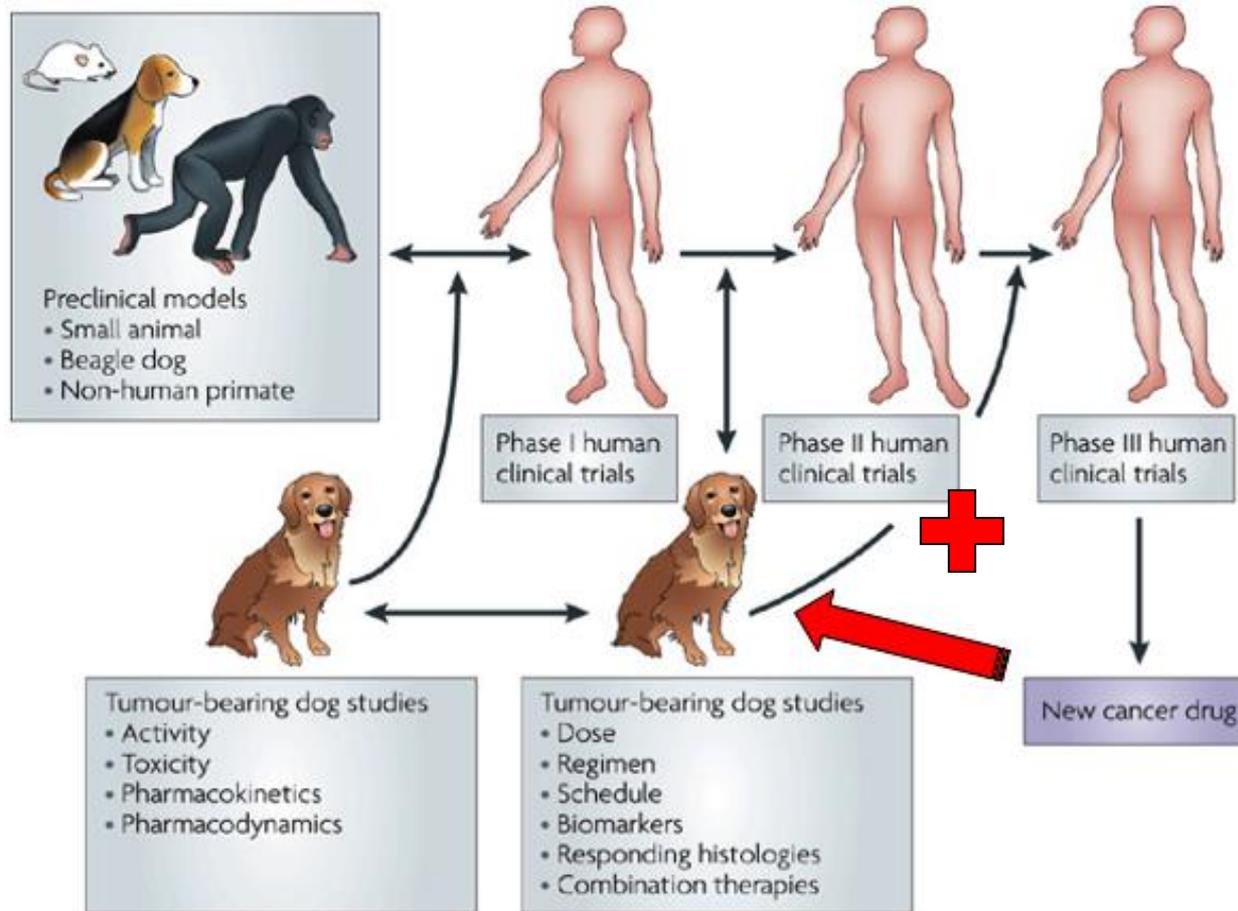
CONSORT Statement 2010 Flow Diagram



From Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.

For more information, visit www.consort-statement.org.

Methods to Enhance Bidirectional Flow



Acknowledgements



Comparative Oncology Trials Consortium



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

Rodney Page^{1,*}, 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.