Getting to proof-of-concept: *novel strategies for phase II development*

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Decision making in drug development: *assessing up or out in phase II???*

- Oncology drug development has lowest clinical success rates compared to other therapeutic areas (~ 5%)
- Reduction of phase III failures are dependent, in part, on improvements in phase II development
  - Primary goal in phase II is to determine if compound has sufficient antitumor activity that is worthy of further development
- Advancement to phase III necessitates significant increases in
  - Patient exposure
  - Investigative site involvement
  - Corporate resources
- Goal is to have success 75% of time compound enters phase III

What is the "burden of proof" from phase II that will sustain a high success rate?

Nat Rev, Drug Discovery 3:711 (2004)

Phase II in era of cytotoxic therapy

Single arm, modest size (30 -50 pts), with population defined by histological tumor types

- Primary endpoint is response rate: direct measurement of tumor size reduction (radiologically)
  - Criteria are established and universally accepted (although they have evolved with “RECIST” criteria)
  - Rapid endpoint (assessed after 2 cycles)
  - Estimate magnitude of treatment effect by comparison to historical controls
  - Efficiently eliminates inactive agents (2-stage designs with 14 or 19 pts)

- Methodological Limitations
  - Differing phase II and phase III endpoints (RR vs survival)
  - Inability to rigorously evaluate historical controls as comparators
  - Patient/tumor heterogeneity, sampling bias
  - Evolving standards of care (surgery, supportive care, imaging)

Innovations in phase II design: *randomized trials*

- CFR lists phase II studies as “controlled clinical studies”
- Benefits
  - Addition of concurrent control arm addresses many issues of historical controls (heterogeneity, selection bias)
  - Allows more accurate estimation of time-to-event variables (PFS, OS)
  - Better suited for “add-on” therapies (A + B vs B) where control is active

- Limitations
  - Requires an average of 2 -3 times # patients (increased cost, time)
  - Not suitable for “screening trials”
  - Substantial error rates decision-making depending how ? and ? are set
  - Insufficient size for randomization to adequately balance arms

Lack of compelling data that decision making is improved (fewer phase III failures) by their use

JCO: 28: 2642 (2010)

Innovations in phase II design: *tumor size as continuous variable*

- Response criteria have traditionally been treated as a discontinuous variable and often dichotomized
  - Partial response included 30% reduction and 95% reduction
  - No response included 20% reduction and 10% increase
- Quantitative models predictive of outcome (survival) have been developed using tumor size at baseline and after 2 cycles (8 weeks) of therapy
  - Based on large phase III datasets
  - Appear to be independent of therapy (ie, cytotoxic or biologic)
  - Maybe prospectively applied to estimate OS
- Models have been published or developed for several common solid tumors (NSCLC – FDA)

Clin Pharm Ther 86: 167 (2009)

Additional Innovations in phase II design

- Adaptive designs – Bayesian methods to adaptively randomize between treatment arms with higher success rates progressively receiving a greater percentage of patients (I-SPY trial)

- Randomized Discontinuation – Patients who achieve stable disease are randomized to treatment vs placebo to observe rates of progression between arms

- Multiple Histology Designs – Allows enrollment for multiple biologic subtypes which allows for analysis of individual histologies and across all tumor types