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Journal of Clinical Oncology Perspective on Phase II Trial Design

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Disclaimer

These viewpoints and opinions are my own and do not necessary reflect those of JCO or the American Society of Clinical Oncology

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About JCO

- Mission
  - JCO is the primary forum of scientific discourse for the American Society of Clinical Oncology (ASCO).
  - JCO strives to publish the highest quality manuscripts dedicated to clinical oncology.
- Impact factor:
  - 18.970
  - 4th among 184 oncology journals
- Acceptance rate
  - ~5000 submissions per year
  - ~15% acceptance rate

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JCO Author Guidelines

- Information for contributors
  - provide direction to authors
  - indicate types of articles of higher priority for JCO readership
- Phase II trials guidance
  - editorial published in July 2009
  - authored by Stephen Cannistra
  - used by editors to guide decisions

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Phase II Trials of the Past

- Handful of available cytotoxic agents
- Single arm Phase II
  - primary mechanism for deciding whether to proceed to a Phase III
  - low false-negative rate (type II error ~ 10%)
  - high false-positive rate (type I error ~ 10%)
  - primary endpoint usually response rate

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Important Changes in Past Decade

- Explosion of available agents
  - target specific pathways
  - not necessarily cytotoxic
- Increased costs of phase III trials
  - financial
  - ethical
  - participant burden
  - opportunity
- High failure rates of phase III trials

  need to increase the “predictiveness” of Phase II trials

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Phase II Trials in New Era

- Single arm Phase II often not ideal
  - use of historical controls
  - response rate often poor surrogate for clinical outcome (survival)
- Increased use of randomization
  - randomized selection design: “pick the winner”
  - randomized comparison design: comparisons made with a control group
  - randomized discontinuation design

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JCO Objective

- To encourage submissions of Phase II studies that have the greatest potential for informing the design of Phase III trials
- Specifically **not** interested in trials for which results
  - are predictable
  - are ambivalent
  - do not move the field forward

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Single Arm Phase II Studies More Likely to be Acceptable

If following are true

- behavior of historical controls stable over time
- low likelihood of response to standard therapy
- desired effect sizes of new agent is large
- cytotoxic mechanism of action
- novel, single agent (first evidence of activity of a new drug class)
- informs the decision to proceed to phase III trial

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Single Arm Phase II Studies More Likely to be Acceptable

Study provides evidence of extraordinary and unanticipated activity

- Novel agent confirms a known class effect
- Provides evidence of extraordinary and unanticipated activity compared to other agents in the same class

  Example: tyrosine kinase inhibitor

  - targets the epidermal growth factor receptor (EGFR), AND
  - overcomes resistance in tumors harboring a T790M mutation in EGFR

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Single Arm Phase II Studies More Likely to be Acceptable

Study is a convincing negative study of agent with prior evidence of activity

- agent previously accepted to be active
- negative study instrumental in halting
  - further investigation of drug
  - ad hoc use of drug in clinical practice
- has correlative pharmacokinetic and pharmacodynamics studies
  - demonstrates drug is bioavailable
  - demonstrates drug affected its intended target

Not of interest if agent belongs to class already shown to be inactive

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Single Arm Phase II Studies More Likely to be Acceptable

Study demonstrates a new, serious, and unanticipated toxicity signal

- agent or combination of agents already accepted as being active
- agent or combination is actively being considered for a phase III trial

NOT of interest if regimen already shown to be inactive

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Single Arm Phase II Studies More Likely to be Acceptable

Study has interesting biomarker that

- validates a mechanism of action
- provides convincing insight into novel predictive markers
- permits enrichment of recruitment of patients most likely to benefit from novel agent

Addition of biomarker correlates does not guarantee high priority for acceptance in absence of other features discussed so far

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Single Arm Phase II Trials **Less** Likely to be Acceptable

- Novel agent used in combination with other agents, unless
  - high-quality preclinical evidence of synergy with other drugs in combination
  - demonstration of very large effect size
- Studies of agents that have been previously studied that report expected results

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Randomized Phase II Studies

Criteria for determining priority for acceptance

- drug novelty
- preclinical rationale for synergy in combination therapies
- convincing effect size
- importance of study in determining whether a phase III will be conducted

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Randomized Phase II Studies

Design guidelines

- prospective statistical plan for evaluating data must be clearly described

  especially for comparison of an experimental arm to control arm

- type I error expected to be 10% or higher
- primary endpoint reflects drug's anticipated mechanism of action
- unplanned analysis of data from randomized phase II strongly discouraged

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Submission Requirements

- Clinical trial must be registered (e.g. clinicaltrials.gov)
- Randomized trials (phase II and III)
  - CONSORT diagram
  - adherence to CONSORT guidelines for reporting a clinical trial
  - redacted protocol that includes:
    - selection of patients (eligibility and ineligibility criteria)
    - schema and treatment plan (including dosing schedule)
    - rules for dose modification
    - measurement of treatment effect (e.g. response criteria, definitions of response and survival, and methods of measurement)
    - reasons for early cessation of trial therapy
    - objectives and entire statistical section (including endpoints)

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Summary

- Not all phase II studies are created equal
- Priority given to trials that have the greatest potential for informing the design of phase III trials
- Although easier to achieve high priority with a randomized phase II design
  - some single arm studies can have high priority
  - not all randomized phase II studies have high priority
- See JCO website for more information

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Questions?

Cannistra SA. Phase II Trials in the Journal of Clinical Oncology. JCO 2009; v. 27 (19): 3073-3076