

# **NCIC CTG New Investigators Course: Workshop II**

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NCIC Clinical Trials Group  
NCIC Groupe des essais cliniques



# Objectives

- Review practical aspects of the design of the phase II trial
- Discuss statistical considerations of the phase II trial
- Provide examples of phase II designs used in clinic trials

# Phase II Trials Objectives

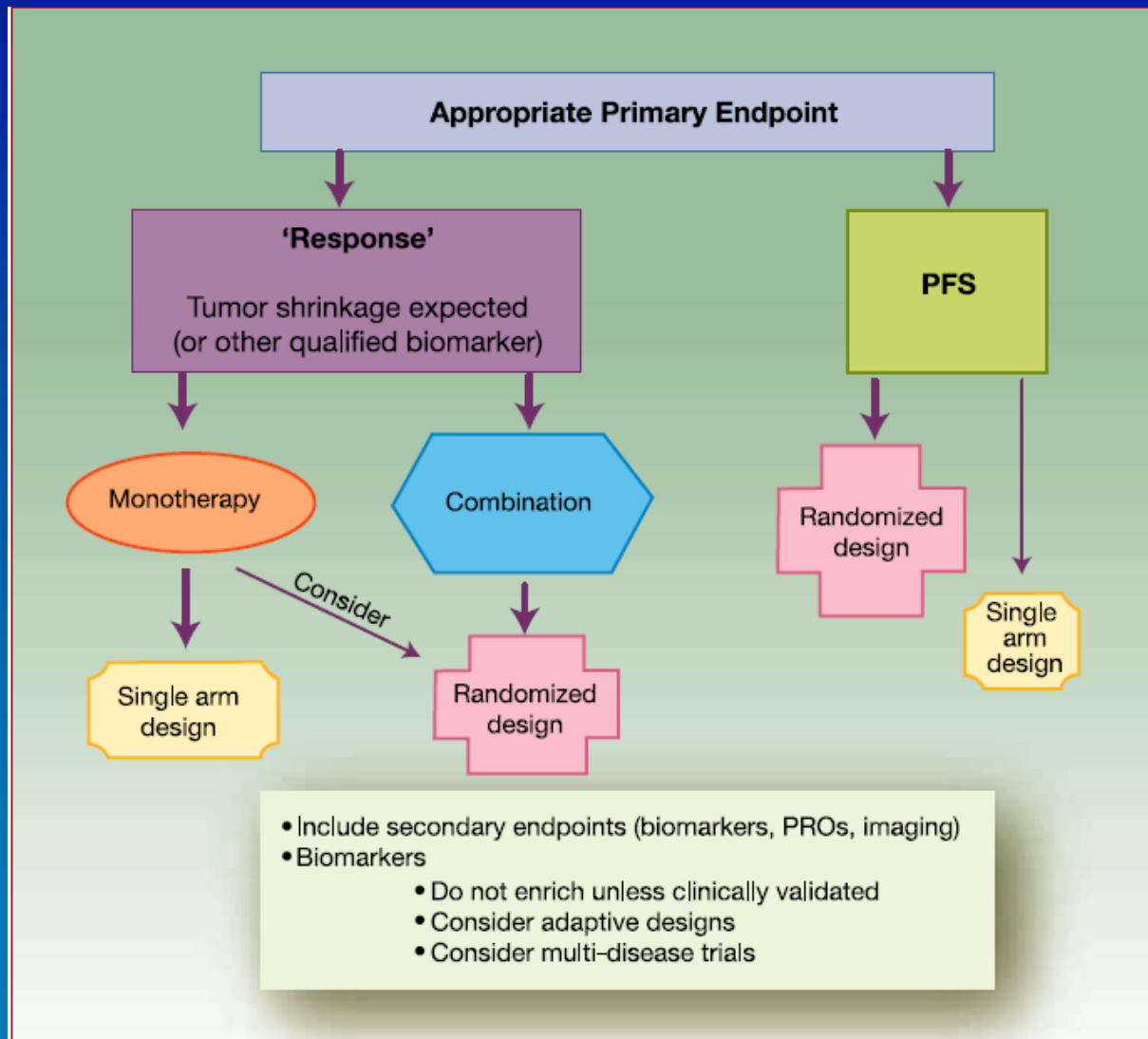
## Primary

- Determine activity of a new treatment in a particular patient population
  - Should the new treatment be evaluated in a phase III clinical trial?

## Secondary

- Toxicity
- Dose/Schedules
- PK
- Correlatives

# Key considerations



L Seymour et al. Clin  
Cancer Res. 2010 Mar  
15;16(6)

# Other Endpoints

1. Multinomial endpoints based on response and early progression rates when response rate are expected to be low.
2. Tumor size as a continuous endpoint.
3. Other endpoints based on biomarkers and imaging

N Dhani et al. Clin Cancer Res. 2009 Mar 15;15(6)

# Statistical Considerations

1. Single arm design: set up null and alternative hypotheses based on thresholds which would declare respectively new treatment as not interesting or interesting.
2. Randomized design: A small hazard ratio (i.e., large difference) is usually used to calculate sample size.
3. Both type I (alpha) and II (beta) errors are usually set as 0.1.

# Examples

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# Scenario 1

- **Phase I trial of a novel agent targeted against receptor for TGFB demonstrated prolonged stable disease in 2 patients with mesothelioma**
- **Based on this finding, investigators wish to evaluate the potential efficacy of this novel agent in mesothelioma further**



# What are the next questions to consider?



# What are the next questions to consider?

- **Endpoint?**
  - Response rate
  - Time to event e.g. PFS
- **Single arm or randomized?**

# Statistics

- The minimum response rate for interest for further study as a single agent is 10%. The agent will be considered as interesting if its true response rate is 30% or higher.
- The optimal two-stage design of Simon [Simon 1989] will be used which allows the study to be terminated after registration of 16 patients if disappointing results are observed.
- Stage I of accrual: Accrue 16 response evaluable patients. If 2 or more objective responses are observed, proceed to stage II.
- Stage II of accrual: Accrue an additional 10 evaluable patients. Consider this treatment for further study if 5 or more patients with objective responses are observed among the total of 26 evaluable patients. This treatment will be deemed uninteresting if 4 or less objective responses are observed among the 26 evaluable patients.
- For this design, the true  $\alpha=0.10$  and  $\beta=0.097$ . The expected sample size if the null hypothesis is true ( $P=0.10$ ) is 20.8 and probability of 0.52 of stopping after the first stage of accrual.

# Pros and Cons?

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## Scenario 2

- **Preclinical rationale for inhibition of MET for the management of triple negative breast cancer**
- **Investigators wish to evaluate the potential efficacy of this novel agent in triple negative breast cancer**
- **The investigators consider stable disease to be of clinical relevance in this disease**

# What are the next questions to consider?

Endpoint?

Single arm or randomized?



# Statistics

- The drug would be considered as inactive if its response rate is 5% or lower and early progression rate is 60% or higher and as interesting if its response rate is 20% or higher or early progression rate is 40% or lower
- Stage 1 of Accrual: 23 response evaluable patients. If there is  $>1$  response or  $< 17$  early progressions, the trial would proceed to stage 2 of accrual.
- Stage 2 of Accrual: An additional 15 patients will be accrued: We would accept the drug as active if in the final sample of 38 patients there are  $>5$  responses or  $<17$  early progressions observed
- The alpha and beta of this design are respectively 0.08 and 0.1

# Multinomial endpoint

## **Application of a New Multinomial Phase II Stopping Rule Using Response and Early Progression**

By S. Dent, B. Zee, J. Dancey, A. Hanauske, J. Wanders, and E. Eisenhauer

J Clin Oncol. 2002 Jan 15;20(2):599.



# Pros and Cons?

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## Scenario 3

- **Virus that has cytotoxic effects via selective replication of the virus within tumour cells with an activated Ras-signaling pathway**
- **Promising activity when combined with chemotherapy in a phase I trial**
- **Investigators are interested to evaluate the agent in combination with chemotherapy in NSCLC**

# What are the next questions to consider?

Endpoint?

Single arm or randomized?



# Statistics

- The primary endpoint of the study is progression free survival
- The expected progression free survival for standard therapy is 4.5 months.
- With a total sample size of 150 accrued in around 21 months and followed for 6 months, we will have 90% power to detect a difference between two combined treatment groups in PFS from 4.5 to 7.7 months (i.e. hazard ratio of 0.59) with a two-sided alpha 0.1.

# Pros and Cons

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## Scenario 4

- **Virus that has cytotoxic effects via selective replication of the virus within tumour cells with an activated Ras-signaling pathway**
- **Promising activity when combined with chemotherapy in a phase I trial**
- **Investigators are interested to evaluate the agent in combination with chemotherapy in prostate cancer**

## Non-comparative phase II

- The clinical trial will accrue up to 80 evaluable patients (40 per arm).
- The primary analysis will be performed for the patients randomized in the virus plus docetaxel group. If 16 or more patients in the virus plus docetaxel group are progression free at 12 weeks, accept virus plus docetaxel as worthy of further study.
- The procedure described above tests the null hypothesis that the 12 week progression rate for virus plus docetaxel  $> 70\%$  versus alternative hypotheses that 12 week progression rate is  $< 50\%$ . The alpha and beta levels of this design is respectively 0.11 and 0.08.
- The 12 week progression rate and associated 90% confidence interval for the patients randomized in the docetaxel alone group will also be calculated, which will provide necessary context for the results obtained from virus plus docetaxel group. Although it may have lower power, the comparison of 12 week progression rates between two treatment groups will also be done using the Fisher's exact test.
- With 40 patients randomized to receive docetaxel alone, we will be able to estimate the true progression rate of docetaxel alone at an accuracy that the half length of a 90% confidence interval will be less than 12% when the observed 12 week progression rate is 70%.

# References

- **The design of phase II clinical trials testing cancer therapeutics: consensus recommendations from the clinical trial design task force of the national cancer institute investigational drug steering committee. L Seymour et al. Clin Cancer Res. 2010 Mar 15;16(6)**
- **Design and conduct of phase II studies of targeted anticancer therapy: recommendations from the task force on methodology for the development of innovative cancer therapies (MDICT). Eur J Cancer. 2008 Jan;44(1)**
- **Application of New Multinomial Phase II Stopping Rule Using Response and Early Progression. Dent et al. J Clin Oncol. 2001 Feb 01; 19 (3)**