Canadian Cancer Trials Group

Phase II RCT Study Design Workshop

Francisco E. Vera-Badillo MD / Wendy R. Parulekar MD

Senior Investigators

Canadian Cancer Trials Group

Queen's University, Kingston On

Disclosures

We have no relevant disclosures to make for this talk

Phases of Drug Development

Preclinical work
- Laboratory/animal models

Phase I
- Determine dose and preliminary toxicity
- Sample size – low tens

Phase II
- **Establish intermediate efficacy**
- **Gain further toxicity information**
- **Sample size – high tens to hundreds**

Phase III
- Validate efficacy and obtain further toxicity information
- Sample size – hundreds to thousands

Phase IV
- Post-marketing surveillance

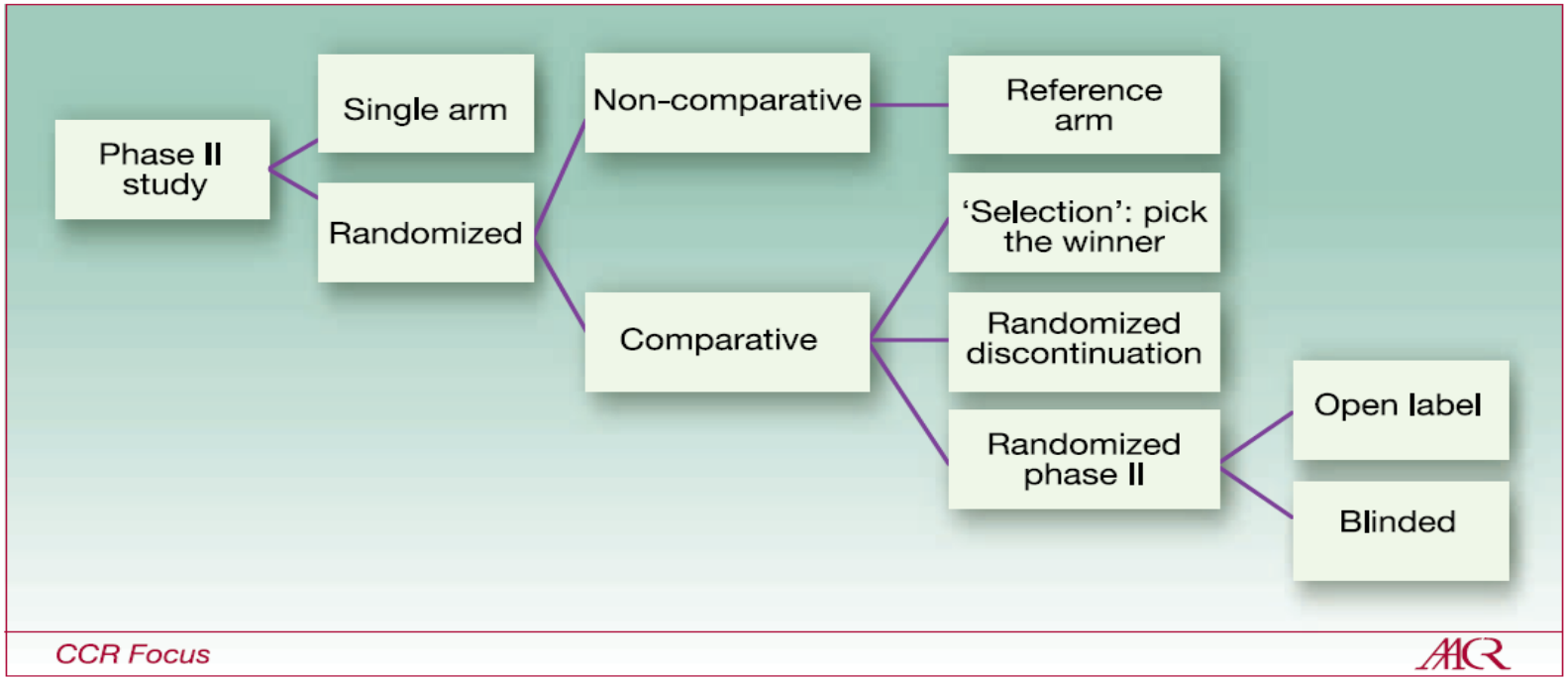
Canadian Cancer Trials Group

Brown et al Br J Cancer 2011;105:194-199

Why are Phase II Trials (Very) Relevant

- Initial estimate of antitumour activity (RR, CB, PFS…)
- Limited exposure to useless drugs.
- Select the drug/regimen/dosing more likely to succeed in a phase III trial RCT.
- Current pressures:
  - *Limited financial and human resources*
  - *Huge number of promising drugs*
    - *Schedules*
    - *Dosing, etc…*

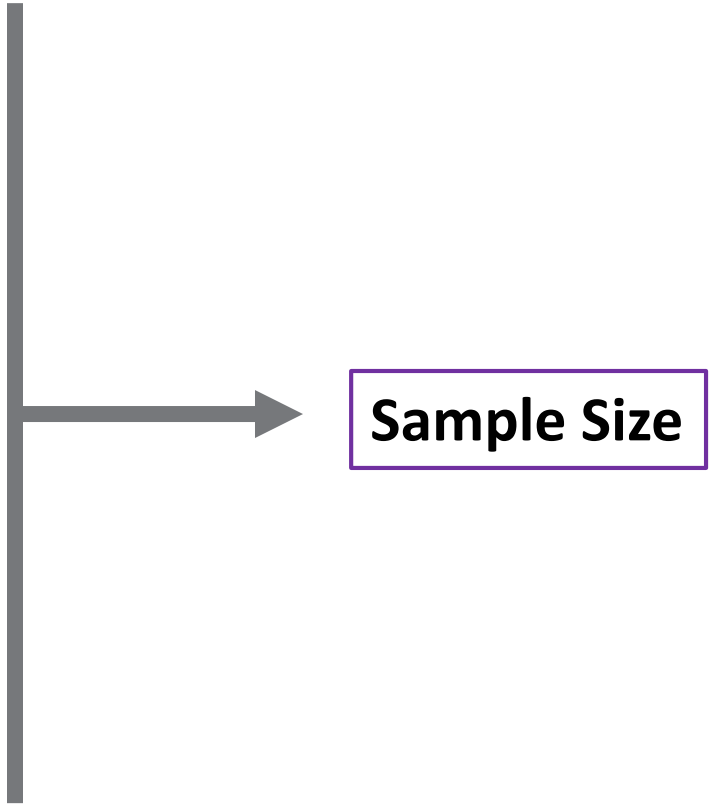
Classification of Phase II Studies



Clin Cancer Res; 16(6) March 15, 2010

Statistical Parameters Driving Clinical Trials

- α:
  - Type I error,
  - Probability of a **false-positive** result.
- β:
  - Type II error,
  - Probability of a false-negative results.
- δ:
  - Targeted difference or,
  - Targeted effect size.



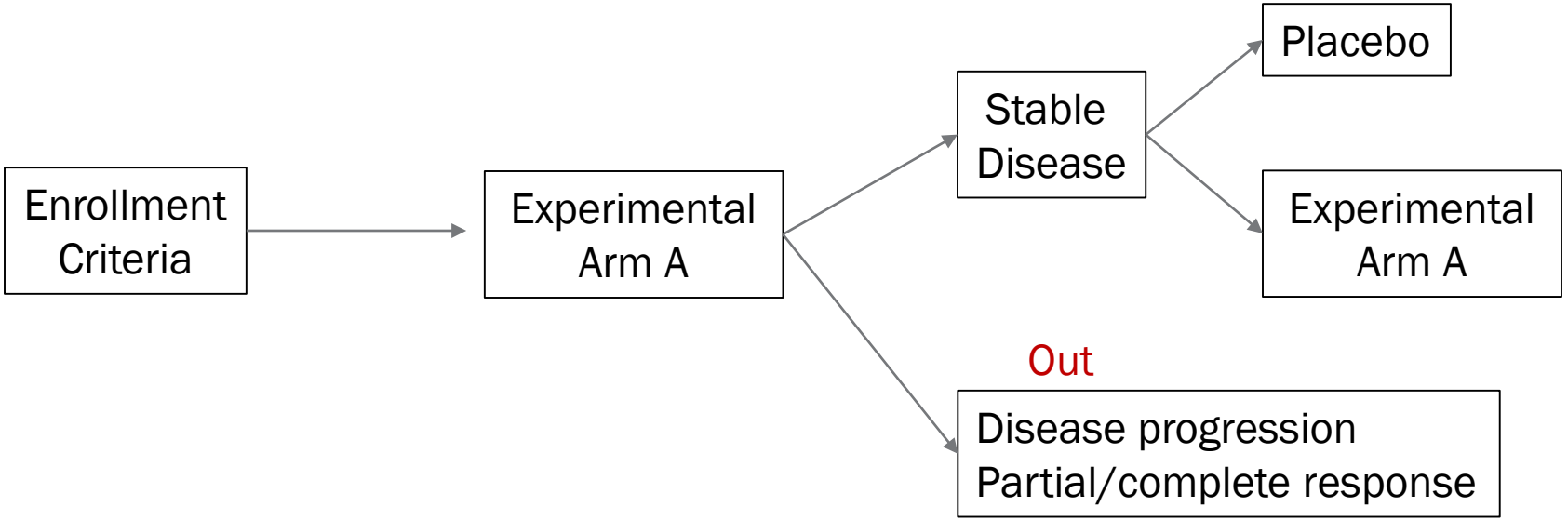
Phase II RCTs

1. Randomized Discontinuation Design

2. Randomized Selection Designs: “Pick the winner”

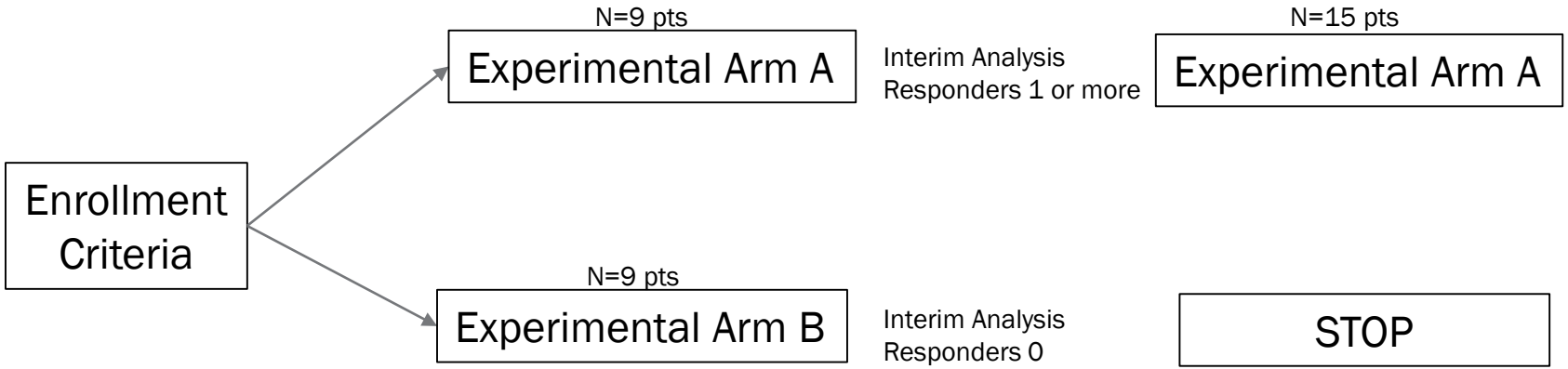
3. Randomized Screening Designs: “Direct comparison (HR)”

Randomized Discontinuation Design



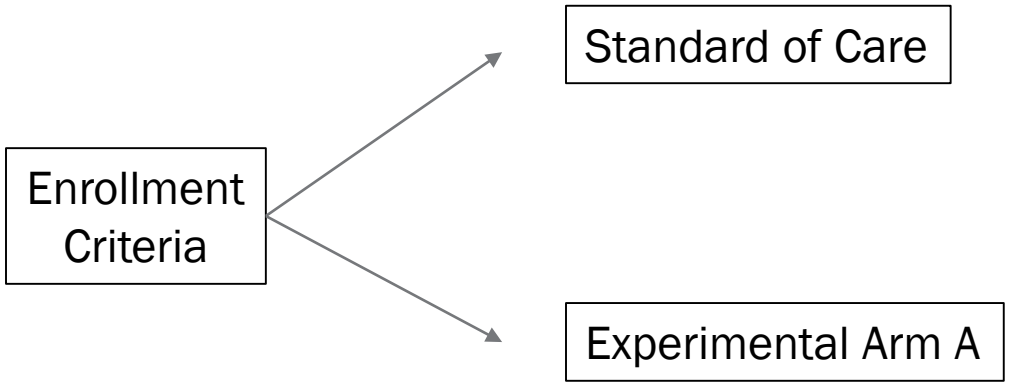
- Study design for cytostatic agents: eg TKIs
- Design helps to distinguish treatment effect vs indolent disease
- Sample size smaller vs all comers

Randomized Selection Designs: “Pick the Winner”



- Aim: select the most promising experimental regimen among other similar regimens
- Scenarios: different modes of drug administration or dosing schedules, comparing different experimental regimens (usually added to core regimen)
- Results are ranked by efficacy and safety
- THIS IS NOT a non-Inferiority design

Randomized Screening Designs: “Direct comparison”



- Preliminary and **non-definitive** comparison
- Prioritize experimental regimens
- Use of an intermediate end point (RR or PFS)
- Reasonable sample size: α: 0.20; β: 0.20 and δ: target difference 20% (HR 1.5)*

Canadian Cancer Trials Group

*Rubinstein, et al J Clin Oncol 2005; 23:7199-7206

Canadian Cancer Trials Group

Scenarios for Phase II Study Design In Oncology Drug Development

Teams

Scenario #1 Vaccine A	Scenario #2 PDL-1 and CTL-4
TEAM #1	**TEAM #2**
Joanne Yu Dan Breadner Jonatha Noujamin Steven Yip Nidhi Kumar Tyagi	Renee Lester Geordie Linford Benjamin Mou Arjun Law Ali Hosni
TEAM #3	**TEAM #4**
Yin Wang Bethany Monteith Daniel Khalaf Ibraheem Othman Barry Aisling	Nafeesa Vawda Guillaume Richard-Carpentier Josee-Lyne Ethier Joel Gray

Canadian Cancer Trials Group

Questions to be answer

- What is your patient population
- Study design: define phase II framework
- Single agent or combination, why?
- Single arm vs multiple arms
- Primary outcome measure
  - Other outcomes

Scenarios in a glance…

- Scenario #1
  - A pharma company is developing a reovirus vaccine, data from the lab and phase I suggest can be potentially active in prostate.
  - Lab suggest that combining the drug with a taxane improves efficacy.

- Scenario #2
  - 2 previous phase III trials with ipilimumab negative, but a pharma company has a CTL-4 and a PD-L1 and they would like to test their drugs in prostate cancer.
  - Correlatives of patients treated with Enza suggest there is a higher PD-L1 expression at the time of progression (Chi, et al).

Experimental Drug #1
Team 1

- **Vaccine A** is a Dearing strain of reovirus serotype 3, with demonstrated in vitro and in vivo activity in many cancers including prostate cancer *[Coffey 1998]*.
- Reovirus has an inherent propensity to preferentially infect and destroy cancer cells through exploitation of activated Ras pathway and downstream elements *[Strong 1998]*.
- Thus it appears to have minimal human toxicity and its human safety and potential efficacy have been demonstrated with >360 patients treated on clinical trials to date.

Background II

- In the setting of prostate cancer, reovirus has demonstrated potent antitumour activity against several prostate cancer cell lines in the SCID/NOD mouse model *[Coffey 1998]*.
- A phase I trial of intraprostatic reovirus injections prior to prostatectomy demonstrated tumour restricted virus uptake with no associated toxicity, and pathologic changes indicating response (i.e. inflammation, apoptosis, necrosis) *[Thirukkumaran 2010]*.
- A recently published phase I trial evaluating the combination of docetaxel with reovirus in 24 patients demonstrated excellent tolerability of the combination up to the RP2D *[Comins 2010]*. Of 16 evaluable patients there was 1 CR, 3 PR and 10 patients with stable disease *[Comins 2010]*.

Background III

- Reovirus has been shown *in vitro* to have synergistic cytotoxic activity with microtubule targeting agents, and especially taxanes *[Sei 2009]*.
- Preclinical data suggests that the assembly of viral replication complexes occurs in association with microtubules *[Broering 2002]*.
- Furthermore, the administration of systemic chemotherapy has been shown to dramatically decrease the levels of neutralizing antibodies to reovirus *[Qiao 2008]* which represents one of the major obstacles to effective oncolytic virus therapy.
- The combination of reolysin with microtubule stabilizing agents such as taxanes is therefore an obvious area of interest. Given that docetaxel is the only chemotherapy that has shown a survival benefit in first line treatment of mCRPC, the combination of reolysin with docetaxel in this disease is a very appealing one for further study.

Experimental Drugs #2 and 3
Team #2

- A PDL-1 inhibitor and a CTL-4 inhibitor from same company are offered to be tested in a phase II trial.
- Combination of anti-PD-L1 and anti-CTLA-4 is a promising approach because of non-redundant pathway blockade and synergy based on preclinical data as well as emergent clinical data, including in unresectable or metastatic melanoma and NSCLC where increase responses were observed with the combination although incremental toxicity is a concern *[Pardoll 2012; Antonia 2015]*.

Background II

- It has been described that PD-L1 becomes highly expressed in enzalutamide resistant prostate cancer and patients progressing on enzalutamide had significantly increased PD-L1/2+ dendritic cells (DC) in blood compared to those naïve or responding to treatment *[Bishop 2015]*.
- These data support previous pre-clinical results, in which significantly increased circulating PD-L1/2+ DCs and a high frequency of PD-1+T cells in mice bearing enzalutamide-resistant (ENZ-R) tumours were found. ENZA-R tumours expressed significantly increased levels of tumour-intrinsic PD-L1. The expression of PD-L1 on ENZ-R cells, or the ability to modulate PD-L1/2+ DC frequency, was unique to ENZ-R cell lines and xenografts that did not show classical activation of the androgen receptor.
- These results suggest that ENZ resistance is associated with the strong expression of anti-PD-1 therapy targets in circulating immune cells both in patients and pre-clinical models

Background III

- We hypothesize that mCRPC progressing after therapy with ENZ or abiraterone may be more sensitive to PD-1/PD-L1 blockade.

- With this rationale, we plan a randomized trial in patients with mCRPC progressing after enzalutamide and/or abiraterone acetate to evaluate the antitumour activity of PD-L1 alone or in combination with CTL-4.

Note

- Please, feel free to ask any specific questions you may related the scenarios you are working on.

Time for Presentation!

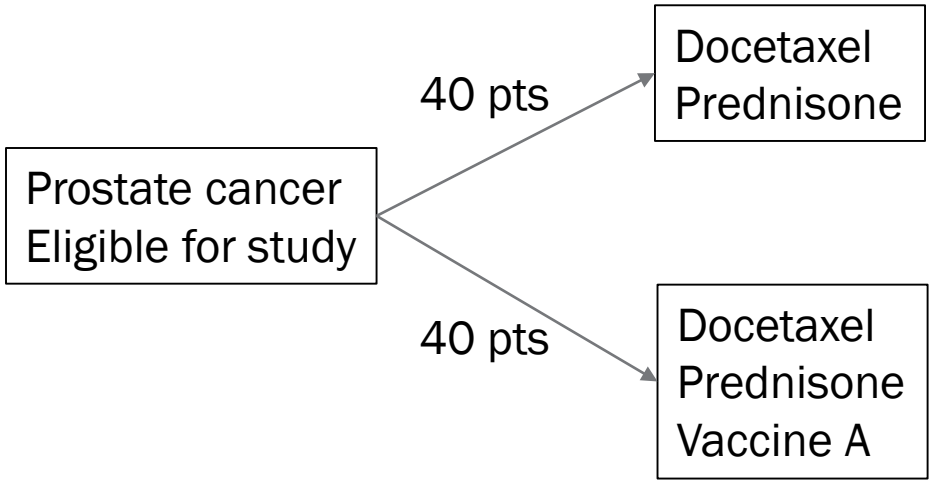
Canadian Cancer Trials Group

Canadian Cancer Trials Group

What CCTG did?...

CCTG Trial Design Proposals

- Experimental Drug #1 – Vaccine A
- Randomized screening design.



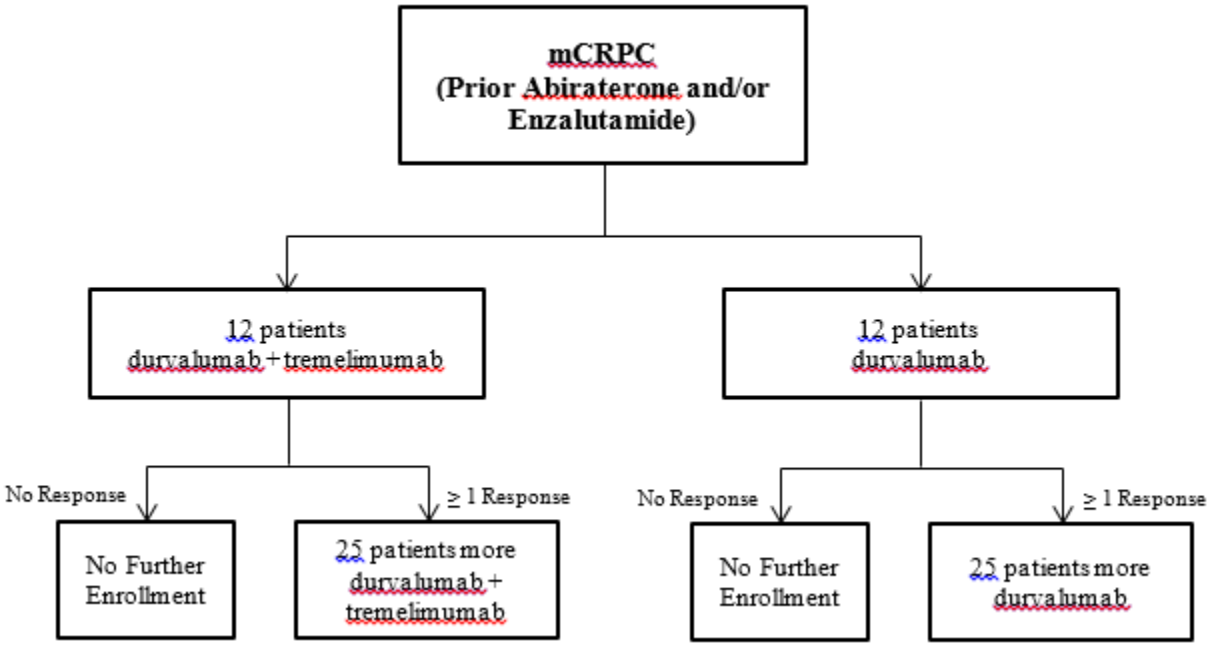
Canadian Cancer Trials Group

Statistical Consideration

- The primary objective of the study is lack of disease progression measured at 12 weeks.
- If 16 or more patients in the reolysin plus docetaxel group are progression free at 12 weeks, accept reolysin plus docetaxel as worthy of further study.
- H0: 12 week progression rate for reolysin plus docetaxel > 70%
- H1: 12 week progression rate is < 50%.
- The probability of concluding the reolysin plus docetaxel is interesting when it is not active, is 0.11;
- The probability of concluding the reolysin plus docetaxel is interesting when it is active, is 0.92.

CCTG Trial Design Proposals

- Experimental Drugs #2 and 3 – PD-L1 and CTL-4
- Randomized selection design.



Canadian Cancer Trials Group

Statistical Consideration

- The primary objective of the study is objective response rate (RECIST 1.1).
- A Simon's optimal two-stage design will be employed for both treatment arms.
- An objective response rate in either arm of 5% or less would not be of interest for further study (null hypothesis).
- If the objective response rate for either cohort were 20% or greater, then this would be considered of interest to further evaluate in larger trials (alternative hypothesis).
- Using an alpha error of 0.1 and a beta error of 0.1, 12 patients per arm will be initially accrued to stage 1. If 1 or more patients had objective response rate on either arm at end of stage 1, the arm will be expanded to a total of 37 evaluable patients. If ≥ 4 measurable responses are observed from these 37 patients in an arm then that arm would be considered for further testing in phase III trials.

Canadian Cancer Trials Group

Time for discussion