Experiences in the Design and Implementation of Phase II Trials in Chronic Lymphocytic Leukaemia

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Contents

- Introduction
- Discussion of phase II trials:
  - CLL201 (2004)
  - CLL207 (2007)
  - ADMIRE and ARCTIC (2008)
  - COSMIC (2012)
- Summary

Introduction

- Chronic Lymphocytic Leukaemia is a terminal haematological cancer, but median survival times are fairly good and improving
- Therapies are continuing to advance rapidly
- Phase II trials aim to assess the **activity** of emerging therapies within different CLL populations
- Provides ideal phase II scenario:

  – which new therapies to take forward in which populations to large phase III trials to determine **efficacy**?

Leeds CTRU Experience

- Five phase II trials for patients with Chronic Lymphocytic Leukaemia since 2004
- Used proven surrogate endpoint of **response** to therapy as a practical short term prognostic marker for survival
- Also used the **level of disease** remaining after treatment as a secondary prognostic measure
- This presentation aims to give an overview of the choices and learning experiences in these trials

CLL201 (2004)

- Adding a monoclonal antibody to standard chemotherapy
- Single arm design using Gehan's two-stage approach to reduce the sample size needed in the case of early signs of efficacy
- Randomised to current standard therapy for internal consistency

Stage I – 4 patients No. of responses observed in the experimental arm	No. of patients required for stage II (per arm)
1	21
2	15
3	3
4	0

- Stage I is after 4 patients to determine to numbers needed in stage II.
- If all of the first 4 patients respond, no further are required. The fewer that respond, the more that are needed for stage II, to a maximum of 25 overall.

Challenges –

- The timing of the stage I analysis without halting recruitment. 9 months to reach primary endpoint.
- Even with 3 or 4 responses, more patients are advantageous to assess toxicity and follow-up for survival to inform the phase III trial

CLL207 (2007)

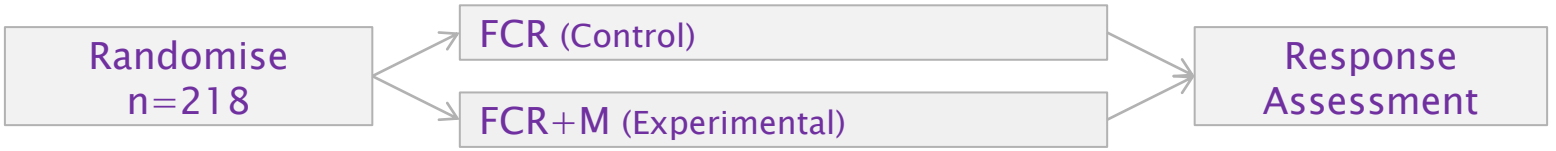
- Consolidation therapy after responding well to initial treatment to eradicate disease
- Single arm using Bryant and Day's two-stage design
- Efficacy (response) and toxicity are joint primary endpoints

Stage	Number Recruited	Unacceptable number to NOT respond	Unacceptable number to experience toxicity
I	24	≤ 5	≥ 9
II	54	≤ 14	≥ 18

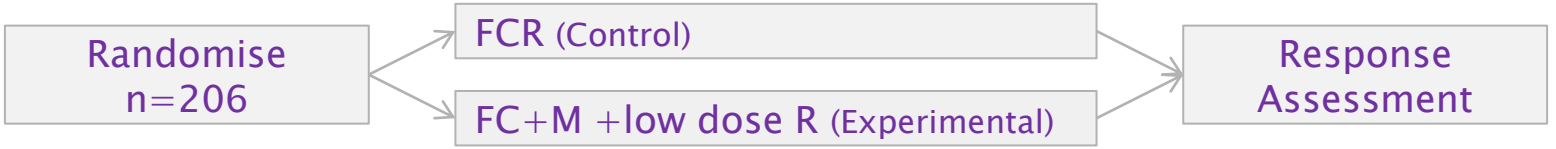
- The two-stage aspect worked well in this trial due to a short treatment duration and assessment time
- Challenges were faced during implementation due to the definitions of unacceptable toxicity and unacceptability bounds, and the overlap with the role of the Data Monitoring Committee
- A phase III trial randomising the treatment against the current standard of no therapy is due to start recruitment soon

ARCTIC and ADMIRE (2008)

- Two large, randomised phase IIb sister trials, informed by the CLL201 trial
- Formally powered to compare responses between treatment arms
- ADMIRE: 80% power to detect a 20% improvement by adding M



- ARCTIC: Non-inferiority design with 80% power to detect inferiority of >10% assessing a lower dose of R



- The formal power calculation is necessary for ARCTIC in particular, as it provides an acceptable certainty of finding the treatment inferior in terms of response before proceeding to a much larger trial to assess longer-term endpoints

ARCTIC and ADMIRE (cont)

Advantages:

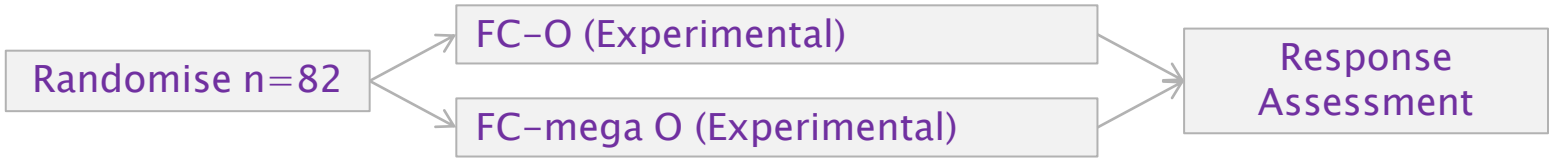
- Over standard phase IIs – more information obtained, reduced chance of an unsuccessful phase III.
- Publishing results – will aid recruitment to the lower dose trial if it proves advantageous.
- Comparison of the experimental arms – the common patient population for the two trials (but in different centres) allows an indirect comparison to further inform the phase III design.

Challenges:

- Convincing reviewers that these were not underpowered phase III trials and we were assessing activity rather than efficacy (a separate phase III would be needed to formally compare long term survival endpoints)
- The trials takes longer to run than standard phase II designs

COSMIC (2012)

- Randomised trial with two experimental arms, assessed independently for activity.
- If applicable, selection criteria applied – most promising therapy to be taken forward for further investigation in a phase III trial.



- 1. A'Hern one-stage design is applied to each arm independently to determine which therapy shows sufficient activity.
  - 10 complete responses (CR) required from 37 patients.
- 2. If both meet the acceptability criteria, Sargent & Goldberg's selection criteria will be applied:
  - selection for activity if number of responses differ by at least 3 (8%) between treatments
  - alternative selection criteria such as safety, tolerability and costs applied if difference in responses <3

Summary

Each phase II trial has a very different design due to the different hypotheses, objectives and therapies.

The designs benefitted from our experiences with previous trials and evolved over time.

Considerations:

- The practicalities of a two-stage design based on time to endpoint
- Balance between larger sample sizes to reduce error and collect more information vs smaller sample sizes to allow a faster assessment of activity
- Whether the trial should be randomised:
  - Are formal comparisons between therapies necessary?
  - Can methods be combined for acceptability and selection?