Phase II clinical trial design and an example of a Flims Workshop protocol

Sarah Brown

Ornella Belvedere

ESMO, Young Oncologists Masterclass

28th September 2012

ctru

Disclosure

- No conflicts of interest to declare

Design and development of phase II trials

Phase II trials in the drug development pathway

- The transition from phase II to III involves the highest risk compared to transition between other phases
  - Phase II to III transition rate = 44%[1]
  - Need to be more sure that moving to phase III is the correct decision
- Act as a screening tool for phase III trials
- Increasing pressure to improve efficiency in the drug development process
- Need to balance speed with making more informed decisions

1. Walker and Newell. Nat Rev Drug Discov, 2009; 8:15-16

Ever-changing treatments

- The way in which treatments work differs both across and within different disease areas
- Need to understand how the treatment under investigation works to enable informed decisions regarding patient populations, endpoints, randomisation, ..., and ultimately in deciding whether or not to proceed to phase III
- Biomarker development may impact patient selection, choice of endpoints, or use of randomisation. Need to use well defined biomarkers

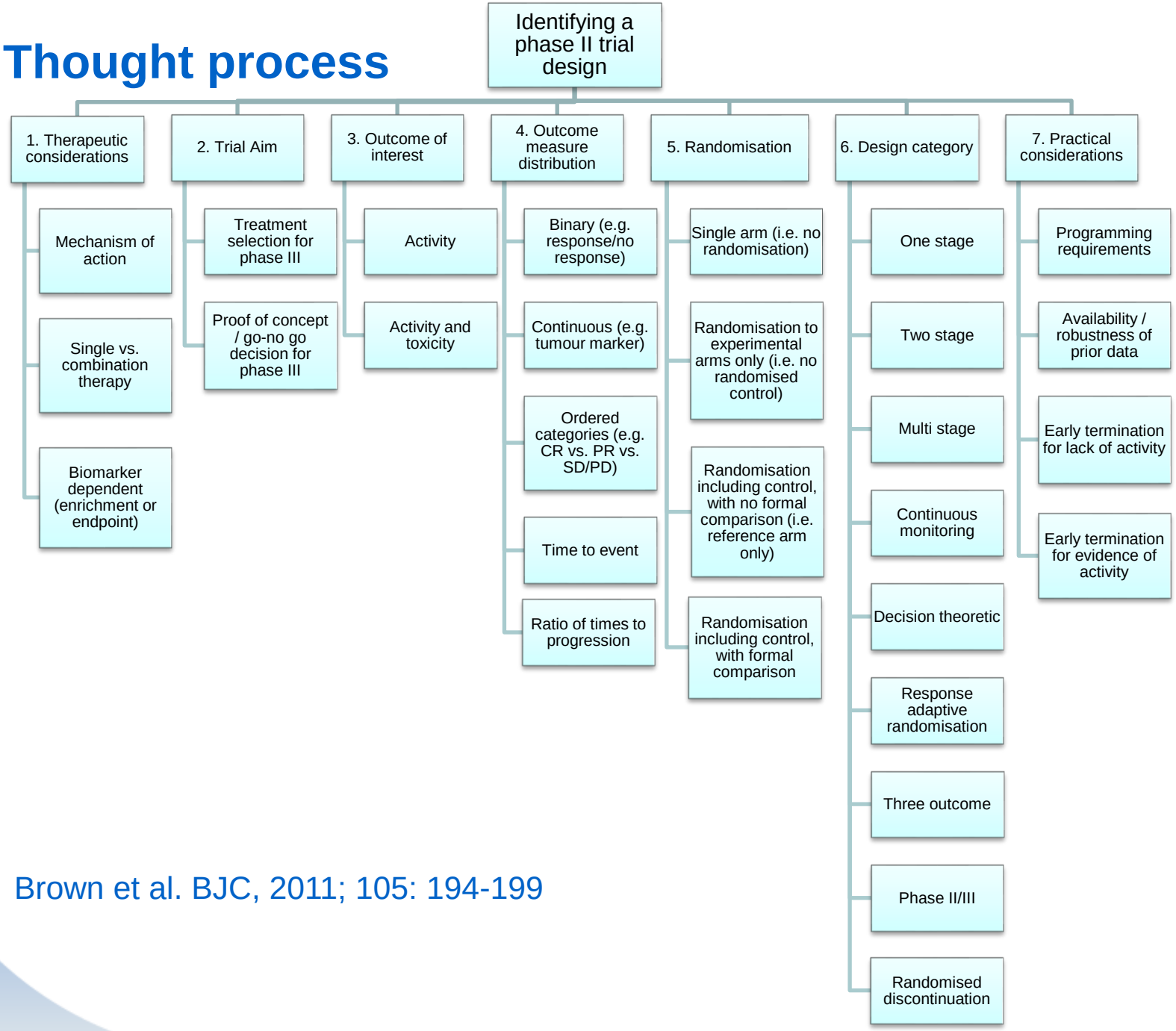
How do we design phase II trials?

- Close collaboration between clinician and statistician is key
- Need discussion early in development of trial
- Multiple options available – early discussion = optimal design
- No one-size fits all design

- Thought process & guidance tool developed to aid researchers in designing phase II trials
  - Key points to consider
  - Library of available phase II designs
  - Based on results of systematic literature review of phase II trial design methodology[1]

1. Brown et al. BJC, 2011; 105: 194-199

Thought process



Brown et al. BJC, 2011; 105: 194-199

Key points for consideration

- 1. Therapeutic considerations
  - Mechanism of action
  - Single vs. combination therapy
  - Biomarker dependent (enrichment or endpoint)

- 2. Trial aim
  - Treatment selection for phase III
  - Proof of concept / go-no go decision for phase III

- 3. Outcome of primary interest
  - Activity
  - Activity and toxicity

Points for consideration contd.

- 4. Endpoint distribution
  - Binary; Continuous; Ordered categories; Time to event; Ratio of times to progression

- 5. Randomisation
  - Single arm
  - Randomisation to experimental arms only
  - Randomisation including control, no formal comparison
  - Randomisation including control, formal comparison

Points for consideration contd.

- 6. Design category
  - One stage; two stage; multi stage; three outcome; continuous monitoring; response adaptive randomisation; decision theoretic; phase II/III; randomised discontinuation;

- 7. Practical considerations
  - Programming requirements
  - Availability of data
  - Early termination

Identifying designs

- Library of statistical designs incorporated to identify those that fit the researcher-defined criteria
- May be numerous designs available:
  - Apply practical consideration
  - Could incorporate past experience – easy to go with what we know, but could a new design be more efficient?
  - Investigate via simulation

Speed vs. reliability

- Often need a trial design NOW, limiting the time available to thoroughly put into practice the thought processes and simulations needed to explore all options
- Taking time to design the trial appropriately ensures more informed decisions can be made regarding moving to phase III

  Investment at design stage = quality of results

- Phase II trials may need to be larger (and therefore longer) to allow better-informed decisions to be made

- Highlights the need for clinician and statistician interaction as early in the trial concept process as possible

Example of a Flims Workshop Protocol:

Randomized phase II study of docetaxel/oxaliplatin vs. docetaxel in previously treated non-small cell lung cancer patients

Alpe adria Thoracic Oncology Multidisciplinary GROUP

ctru

Background

- Single agent docetaxel and pemetrexed are approved, with modest activity as 2nd line treatment for NSCLC[1,2]
- To date, no combination regimen has proven superior to single agent chemotherapy as 2nd line treatment[3]
- Oxaliplatin is non cross-resistant with, and may be more effective than, cisplatin/carboplatin
- The feasibility of combining oxaliplatin with docetaxel has previously been established[4]

1 Shepherd FA et al, J Clin Oncol 2000;18:2095 - 2 Hanna N et al, J Clin Oncol 2004;22:1589
3 Di Maio M et al, J Clin Oncol 2009;27:1836 - 4 Kouroussis C et al, Anticancer Res 2003;23:785

Original proposal outline

- **Title:** Phase II study of docetaxel/oxaliplatin in 2nd line NSCLC
- **Main objective:** Determine the activity of docetaxel/oxaliplatin in 2nd line NSCLC
- **Endpoints:** RR (primary); toxicity, time-to-progression, survival (secondary)
- **Study design:** Single arm phase II trial according to Simon's two stage design (18 + 18 pts)

Points to consider

1. Cytotoxic combination therapy; expect tumour shrinkage; no known biomarkers
2. Go/no go decision for phase III
3. Primarily interested in activity – previous studies of feasibility

4. From 1), primary endpoint = response
5. i) From 1), combination therapy – want to ensure any activity is due to addition of oxaliplatin;
   ii) Historical data available for docetaxel alone
   iii) Small number of sites, few patients available

   Randomisation with no formal comparison

6. i) safety previously been shown; don't want to incorporate formal stopping rules through multi-stages;
   ii) Small number of sites, few patients available

Final study design

- Promoted and conducted by Italian lung cancer group - ATOM

Stage wIIIB-IV NSCLC

Age ≥ 18 and < 70 yr

ECOG PS 0 – 1

1 prior chemo regimen

No prior docetaxel or oxaliplatin

Measurable disease

CNS mets allowed, if symptoms controlled for ≥ 4 weeks

Periph neuropathy < gr 2

R

Docetaxel 75 mg/m^2 d1
Oxaliplatin 70 mg/m^2 d2

Docetaxel 75 mg/m^2 d1

Both arms every 3 weeks up to 6 cycles

ctru

Statistical design

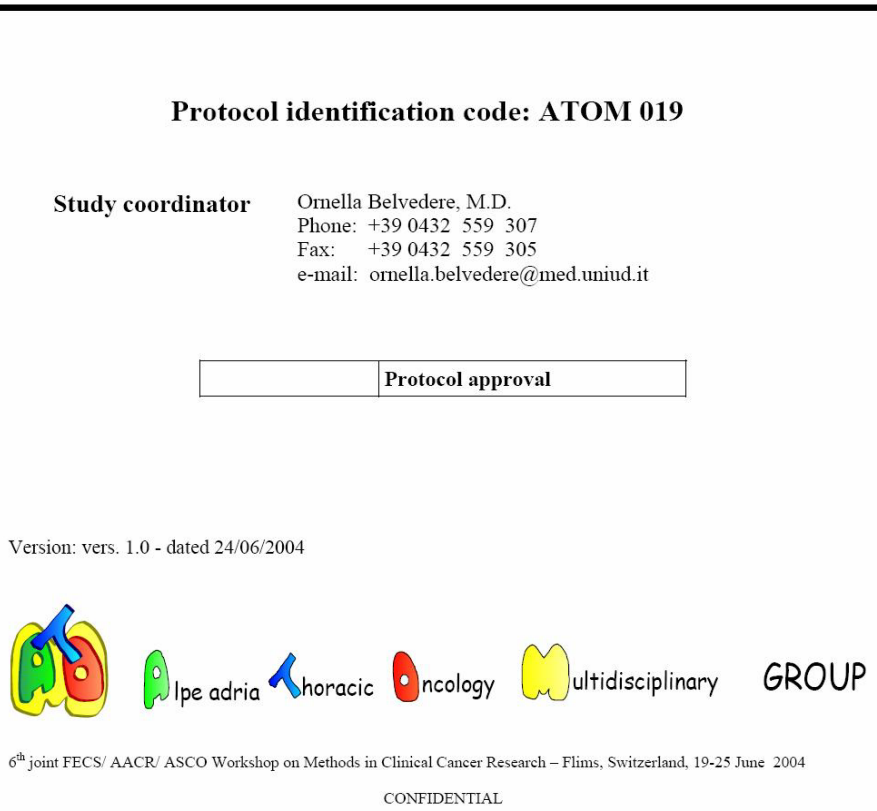
- Non-comparative randomized phase II trial
- One-stage three-outcome phase II study design[1]
- Ho: RR ≤ 10%, HA: RR ≥ 30%; α error 5%; β error 10%
- 21 evaluable patients needed in each arm to reject an ineffective treatment or correctly accept an effective treatment with a probability of ≥ 80%
  - if ≤ 3 responses, DO is declared ineffective
  - if exactly 4 responses, the study is inconclusive
  - if ≥ 5 responses, DO is declared effective

1 Sargent DJ et al, Control Clin Trials 2001;22:117

During the workshop

- Week-long workshop
- **Develop full study protocol**
- Advice and expertise from Flims faculty members

- Hard work!!



Randomized phase II trial of second-line chemotherapy with oxaliplatin and docetaxel vs. docetaxel in patients with advanced non-small cell lung cancer

Protocol identification code: ATOM 019

Study coordinator Ornella Belvedere, M.D.
Phone: +39 0432 559 307
Fax: +39 0432 559 305
e-mail: ornella.belvedere@med.uniud.it

	Protocol approval

Version: vers. 1.0 - dated 24/06/2004

Alpe adria Thoracic Oncology Multidisciplinary GROUP

6th joint FECS/ AACR/ ASCO Workshop on Methods in Clinical Cancer Research – Flims, Switzerland, 19-25 June 2004

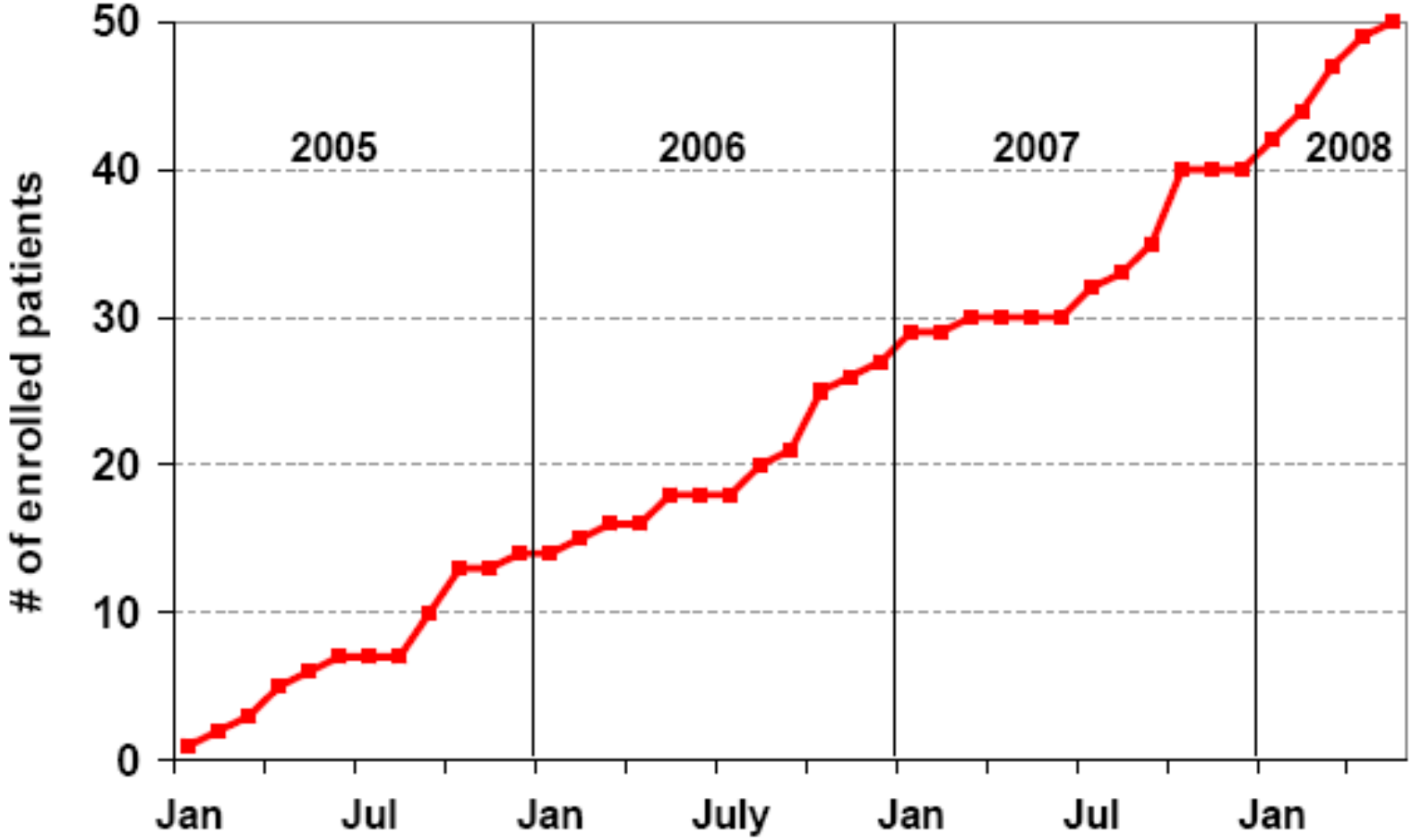
CONFIDENTIAL

Experience

- You are the Chief Investigator
- You are responsible for:
  - Ensuring that an investigation is conducted according to
    - » study protocol
    - » ethics requirements
    - » all applicable national & institutional regulations
  - Control of all drugs/agents under investigation
  - Protecting the rights, safety, and welfare of subjects under the investigator ’s care

- Need to obtain ethics & site approvals, develop CRFs, manage grant, develop database, ….

Patient accrual



EUROPEAN JOURNAL OF CANCER 47 (2011) 1653–1659

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

A randomised phase II study of docetaxel/oxaliplatin and docetaxel in patients with previously treated non-small cell lung cancer: An Alpe–Adria Thoracic Oncology Multidisciplinary group trial (ATOM 019)

Ornella Belvedere [a,b,*], *Alessandro Follador* [a], *Ciro Rossetto* [a], *Valentina Merlo* [a], *Carlotta Defferrari* [c], *Angela M. Sibau* [a], *Marianna Aita* [a], *Maria G. Dal Bello* [c], *Stefano Meduri* [d], *Marica Gaiardo* [a], *Gianpiero Fasola* [a], *Francesco Grossi* [c]

[a] *Department of Medical Oncology, Santa Maria della Misericordia University Hospital, Udine, Italy*
[b] *Leeds Institute of Molecular Medicine and St. James's Institute of Oncology, St. James's University Hospital, Leeds, UK*
[c] *Lung Cancer Unit, National Institute for Cancer Research, Genova, Italy*
[d] *Department of Radiology, Santa Maria della Misericordia University Hospital, Udine, Italy*

Study conclusions[1]

- This trial met its primary endpoint of ≥ 5 responses in patients on the docetaxel plus oxaliplatin (DO) arm
- Toxicities were manageable and as expected in both arms
- PFS and OS were encouraging for DO
- Results warrant further investigation of DO in patients with NSCLC in Phase II/III trials:
  - 2nd line: DO vs docetaxel
  - 1st line: DO vs standard platinum-based regimen

1 Belvedere et al, EJC 2011; 47: 1653-59

Recommendations

- If you are a YO interested in clinical research and have not been to Flims:

  apply… and if you are not selected… apply again!

- If you have already been on the Flims Workshop or if you are a senior oncologist:

  encourage your young colleagues to apply and support them with their application!

ctru

Summary

- Phase II trials continue to pose challenges in their design, with ever changing drug mechanisms, new designs, and time pressures
- A structured thought process allows key points for consideration to be incorporated when designing phase II trials, aiding appropriate trial design and protocol development
- Talk to your statistician early in study conception
- Apply to the Flims Workshop

Thank you for your attention

s.brown@leeds.ac.uk
o.belvedere@leeds.ac.uk