FOCUS4

A molecularly stratified randomised controlled trial programme (and a novel trial design for targeted therapies)

R Kaplan

MRC Clinical Trials Unit at UCL, London
Fundamental challenges in oncology trials

• How can we speed up development and testing, shortening time to patient access?

• How do we assess activity in early phase trials to improve our success rate in novel agent development?

• How can we predict which patients will respond to a new agent/regimen?
Why we need new trial designs

• Many new agents available

• Each takes years to confirm clinical benefit

• Track record of (phase III, registration) success not yet especially good

• Biologic pathways becoming understood
  • biomarker stratification expected to enrich population & improve likelihood of success
  • (but many ‘predictive’ markers not validated)
Can we make strategy more efficient?

- For initial testing
  - Identify informative clinical settings
    - (regardless of whether a good setting for licensing)
  - Biomarker-enrich
    - (can subsequently expand population and stratify)
  - Seek strong signal of activity
    - (ambitious HR)
- Multi-stage trials
- Multi-arm trials (test several agents at once)
- ‘Umbrella’ or ‘rolling’ trial structure
Traditional approach to testing
Multi-arm multi-stage (MAMS) approach
Multi-arm multi-stage (MAMS) approach

Multi-arm
• Test many relevant agents

Multi-stage
• Ask if reasons to *continue* investigating a treatment?
Advantages of MAMS trials

1. Fewer patients
   - Concurrent assessment of agents
   - Randomise from start
   - One seamless trial
   - One protocol → Less bureaucracy

2. Less overall time
Advantages of MAMS trials

3. Increased flexibility

- Adapts to intermediate results
- Focus on more promising arms

Traditional Approach

Phase II

T1

T2

T3

T4

Phase III

C

T1

C

T3

C

T4

Multi-arm, Multi-stage

Phase II

C

T1

T2

T3

T4

Phase III

C

T1

T2

T3

T4
Advantages of MAMS trials

4. Reduced costs

- Limited resources for trials
- Must use fairly and efficiently

Traditional Approach

- Phase II
  - T1
  - T2
  - T3
  - T4

- Phase III
  - C T1
  - C T3
  - C T4

Multi-arm, Multi-stage

- Phase II
  - C T1
  - T2
  - T3
  - T4

- Phase III
  - C T1
  - C T3
  - C T4
STAMPEDE: Enzalutamide plus abiraterone comparison to be activated

Jul-2014: Third new comparison activated
CRC Genomic heterogeneity
(Potentially identify biologically & clinically distinct subgroups)

COIN
N=1874

“All wild-type”
41.8%

KRAS mutant
42.0%

NRAS mutant
3.2%

PIK3CA mutant
12.8%

BRAF mutant
8.7%

7.9

0.1

0.2

0.3

0.5

2.2
Why conventional designs are unsatisfactory

- Usually depend on availability of a validated biomarker
  - and full validation is itself a lengthy process

- Biomarkers are validated at different times and are usually not all ready at once

- Separate biomarker-based trials are inefficient:
  - either many screened patients are not eligible
  - or both marker selected and unselected patients are included
Why conventional designs are unsatisfactory

• Some prospective designs aim to evaluate both a new treatment and a biomarker within one trial
  • ‘biomarker stratified’ design inefficient because need to size trial on the effect in all patients, which is likely to be modest
  • ‘marker by treatment interaction’ design inefficient because need to size on the difference between the effect of the treatment in biomarker + and - patients (an interaction)

FOCUS4 is an attempt to move the field forward on the basis of partially-supported, putative biomarker classification and adapt to developments over time
What is FOCUS4?

- An adaptive enrichment design integrated programme of parallel, molecularly stratified randomised comparisons in patients with advanced/metastatic colorectal ca
  - who are stable or responding to 1st-line chemotherapy
  - it takes advantage of the UK-preferred planned chemo break to test the efficacy of novel agents (vs placebo) before resistance to standard agents occurs
- Intended to encompass all biomarker defined/enriched cohorts, and to be adaptable to new biomarker developments
- ‘Multiplexed markers / multiplexed trials’
- A collaboration between academia & pharma industry
FOCUS4 aims

• To test rationally selected targeted drugs for single agent or combined novel-novel activity
  • as demonstrated by an increase in PFS in the chemotherapy-free interval
  • following first line chemotherapy in biomarker enriched subpopulations

• Phase 2/3 structure: first seeks PFS signal of activity in initial stages; then can continue as a definitive phase 3 trial in any or all of the cohorts, using PFS and OS endpoints
Intermediate endpoints

• Use of intermediate endpoints in agent development – for early proof of principle and go/no-go decisions

• ‘Intermediate’ ≠ ‘surrogate’ for registration
**MRC FOCUS4**

**mCRC**
- First line chemo 16 wks
- Stable/responding

**Diagnostic biopsy**

**Biomarker analysis**

**REGISTER**

**RANDOMISE**

**ALLOCATE**

**Primary endpoint**
- PFS in the interval

**RESTART first line chemo on progression**

- BRAF
  - Novel agent
- PIK3CA
  - Novel agent
- KRAS
  - Novel agent
- All WT
  - Novel agent
- NONE
  - CAP

**rebiopsy**
mCRC
First line chemo 16 wks
Stable/responding

Biomarker analysis

Diagnostic biopsy

REGISTER

BRAF

PIK3CA

KRAS

All WT

NONE

AZD 8931

CAP

Diagnostic biopsy

primary endpoint

PFS

in the interval

restart first line chemo on progression

rebiopsy

ALLOCATE

RANDOMISE

rebiopsy
mCRC First line chemo 16 wks Stable/responding

Diagnostic biopsy

Biomarker analysis

REGISTER

BRAF
PIK3CA
KRAS
ALL WT
NONE

ALLOCATE

RANDOMISE

BRAF PIK3CA KRAS ALL WT NONE

P BRAF I ± MEKi + EGFRi
P PI3K i
P Next agent
P AZD 8931
N CAP

Primary endpoint
PFS in the interval

Restart first line chemo on progression

rebiopsy
mCRC First line chemo 16 wks
Stable/responding

Diagnostic biopsy
Biomarker analysis

REGISTER

BRAF
PIK3CA
KRAS
All WT
NONE

ALLOCATE
RANDOMISE

BRAF I ± MEKi + EGFRi
PI3K i
Test specificity
AZD 8931
CAP

Primary endpoint
PFS in the interval

Restart first line chemo on progression
rebiopsy
FOCUS 4: design considerations

Each biomarker/treatment comparison has 4 stages:

• 2 lack of activity/signal-seeking stages, where randomisation can be ceased (phase II, PFS endpoint)
• 2 efficacy stages (phase III, with PFS and OS endpoints)

If a treatment passes the 2 lack of activity stages (looks promising)

• Aim to assess activity in an ‘unselected cohort’
  • A parallel randomised trial of that treatment, using one or more of the other cohorts in FOCUS4

If treatment does not pass an activity stage, can consider testing new hypotheses or agents
FOCUS4 Adaptive Multi-stage Design

RANDOMISATION

Stage I
Interim analysis for safety and lack of significant activity (LSA) (PFS)

Stage II
Interim analysis for LSA (PFS)

Stage III
Interim analysis for efficacy (PFS)

Stage IV
Interim analysis for efficacy (OS)

Consider testing new hypotheses biomarkers cohorts and agents

Stage III
Test biomarker specificity in non-selected patients

‘phase 2’

‘phase 3’
## Projected patient accrual per stage

<table>
<thead>
<tr>
<th>Molecular cohort</th>
<th>Randomised allocation ratio</th>
<th>Phase</th>
<th>Outcome and stage</th>
<th>Target HR</th>
<th>Max number of events required: total (control arm)</th>
<th>Estimated cumulative analysis time (months)</th>
<th>Max number of pts required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF mutation</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.5</td>
<td>41 (16)</td>
<td>20.4</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.5</td>
<td>76 (28)</td>
<td>32.5</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.5</td>
<td>118 (42)</td>
<td>46.5</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.65</td>
<td>217 (79)</td>
<td>100.4</td>
<td>301</td>
</tr>
<tr>
<td><strong>PIK3CA mutation and/or PTEN loss</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.65</td>
<td>107 (40)</td>
<td>17.0</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.65</td>
<td>197 (71)</td>
<td>26.5</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.65</td>
<td>303 (107)</td>
<td>37.2</td>
<td>373</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.7</td>
<td>289 (109)</td>
<td>54.6</td>
<td>546</td>
</tr>
<tr>
<td><strong>KRAS or NRAS mutation</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.65</td>
<td>109 (41)</td>
<td>16.1</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.65</td>
<td>198 (72)</td>
<td>22.8</td>
<td>273</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.65</td>
<td>302 (107)</td>
<td>31.4</td>
<td>378</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.7</td>
<td>287 (109)</td>
<td>50.6</td>
<td>574</td>
</tr>
<tr>
<td><strong>EGFR dependent</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.65</td>
<td>109 (41)</td>
<td>20.0</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.65</td>
<td>198 (72)</td>
<td>30.6</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.65</td>
<td>301 (107)</td>
<td>42.3</td>
<td>381</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.7</td>
<td>289 (109)</td>
<td>60.8</td>
<td>547</td>
</tr>
</tbody>
</table>
Advantages to FOCUS4 design (1)

- Uses molecularly enriched cohorts – & ambitious HRs – to maximise possibility of detecting promising new treatments and rejecting minimally active ones
- Tests each (presumed) biomarker cohort separately, against its own control (addressing biomarker prognostic effects)
- Does not test cohorts/agents against each other

Based on MAMS design:

- Initial emphasis is phase II in intention (signal seeking)
- But can continue efficiently (seamlessly) into phase III
Advantages to FOCUS4 design (2)

• Allows for study when biomarkers are incompletely characterised and/or not fully validated
• ‘Umbrella’ structure allows for efficient inclusion of less common biomarker cohorts
• Efficient platform for ascertaining specificity of any positive results in relation to biomarker selection used
• Adaptive: allows for efficient incorporation of new information and/or drugs into a large ongoing trial
• FOCUS4-N answers an important maintenance chemo question when some biomarker-selected cohorts are temporarily closed
FOCUS 4: design considerations

• When new external information emerges . . .
  – Biomarker refined
  – Treatment ineffective

• . . . FOCUS 4 can continue with necessary amendment
  – Prospective/retrospective change to an arm
  – Cease further randomisation to an arm

• Adaptive design means that we can do this as a protocol amendment while rest of trial continues

• Tissues and bloods collected to explore
  – Refinement of biomarkers
  – New potential biomarkers
Understanding disease biology
Colorectal Cancer Subtyping Consortium > 4000 cases

Integrated analysis by CRCSC of gene expression profiles suggest 4 consensus molecular subtypes in CRC

CMS1 Right colon, MSI, hypermutation, BRAF mut, immune activation 13%

CMS2: Epithelial, MSS, high CIN, TP53 mut, WNT/MYC pathway activation: left colon 35%

CMS3: Epithelial, CIN/MSI, KRAS mut, MYC ampl, IGFBP2 overexpression 11%

CMS4: Mesenchymal, CIN/MSI, TGFβ/VEGF activation, NOTCH3 overexpression 20%

21% Unclassified: Mixed subtype with variable epithelial-mesenchymal activation?

### CRCSC — Individual groups’ subtypes

<table>
<thead>
<tr>
<th>Surface crypt</th>
<th>Lower crypt</th>
<th>CIMP+</th>
<th>Mesenchymal</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN Immune down</td>
<td>dMMR</td>
<td>KRASm</td>
<td>CSC</td>
<td>CIN Wnt up</td>
</tr>
<tr>
<td>A type</td>
<td></td>
<td>B type</td>
<td></td>
<td>C type</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Goblet</td>
<td>Transit Amplifying</td>
<td>Stem-like</td>
<td>Enterocyte</td>
</tr>
<tr>
<td>CCS1</td>
<td></td>
<td>CCS2</td>
<td></td>
<td>CCS3</td>
</tr>
<tr>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
<td>2.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

- **MSI/CIMP**
- **CIN**
- **Invasive**

FOCUS4 is adaptive in 4 ways

1) Update biomarkers as they evolve

2) Introduce new treatments either in new biomarker defined group or if treatment is inactive

3) Open each comparison to biomarker-negative patients for treatments which show sufficient activity in biomarker-positive patients

4) During times when a comparison is not open, patients will be offered randomisation to FOCUS4-N or another comparison if biologically justified
Lesson 1 - FOCUS4A
Don’t best guess the science!

The context dependency of mutations
Why V600E isn’t V600E
Lesson 2 – FOCUS4B & C
Two pathways are tougher than one
And pertinent models do tell us something
FOCUS4 trial design considerations

Experimental arms

• Trametinib or Dabrafenib + Panitumumab . . . or
• Dabrafenib + Trametinib + Panitumumab

Control arm

• Placebo . . . or
• Continued maintenance chemotherapy

• Assume same target HR for these comparisons as previously; HR=0.5 for PFS (stages 1 to 3) and HR=0.65 for OS (stage 4)
Lesson 3

The criticality of *trying* to keep the control arm contemporary

Maintenance, time out and the CDF
Study design

- SD or better after 6 cycles CAPOX-B
- Observation
- Capecitabine + Bevacizumab
- PD
- Re-introduction CAPOX-B
- PD
- PFS1
- PFS2

- Stratification factors: prior adjuvant therapy, serum LDH, response to induction treatment, WHO PS, institution
- Primary endpoint: PFS2
- PFS2 is considered to be equal to PFS1 for patients in whom CAPOX-B is not reintroduced after PFS1 for any reason

Presented By Miriam Koopman at 2014 ASCO Annual Meeting
Antibodies and the CDF

- Bevacizumab delisted in first line CRC from March 2015.
- Cetuximab and Panitumumab approved in first line combination in RAS wildtype
- Bev approved in second line with FOLFOX
- Cetux / pan approved in third line therapy for RAS wildtype
FOCUS4 Trial Group

**Sponsors - MRC CTU**
- Trial Managers: Cheryl Pugh, Riya Bathia
- Data Manager: Krishna Letchemanan
- Trial Assistant: Helen Fisher
- COG managers: Anna Bara, Lynda Harper
- Statistician: David Fisher
- Project Lead: Louise Brown
- Clinical Research Fellow: Kai-Keen Shiu
- Programme Leads: Rick Kaplan, Max Parmar

**Trial Management Group**
- Overall CIs: Tim Maughan & Richard Wilson
- Trial CIs: Gary Middleton (A), Harpreet Wasan (B), Richard Wilson (C), Richard Adams (D), Tim Maughan (N)
- Safety lead: Will Steward
- Scotland: Leslie Samuel
- NCRN advisors: Gina Dutton & Jane Beety
- Pharmacy: Elizabeth Hodgkinson & Nicola Stoner
- Nurse specialist: Sandie Wellman
- Patient reps: Malcolm & Jan Pope

**Biomarker Specialists**
- Cardiff: Bharat Jasani, Rachel Butler
- Leeds: Phil Quirke, Susan Richman