FOCUS4

A new biomarker-stratified phase 2/3 trial for colorectal cancer (CRC)

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on behalf of the FOCUS4 Group

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 especially good

- Biologic pathways becoming understood → biomarker stratification possible – or even necessary – to enrich population and improve likelihood of success

Why conventional designs unsatisfactory

- Usually depends on availability of a validated biomarker
    - And full validation is another lengthy process
- Biomarkers are validated at different times and are usually not all ready at once
- Each trial is inefficient since many screened patients are not eligible, or both marker selected and unselected patients are included
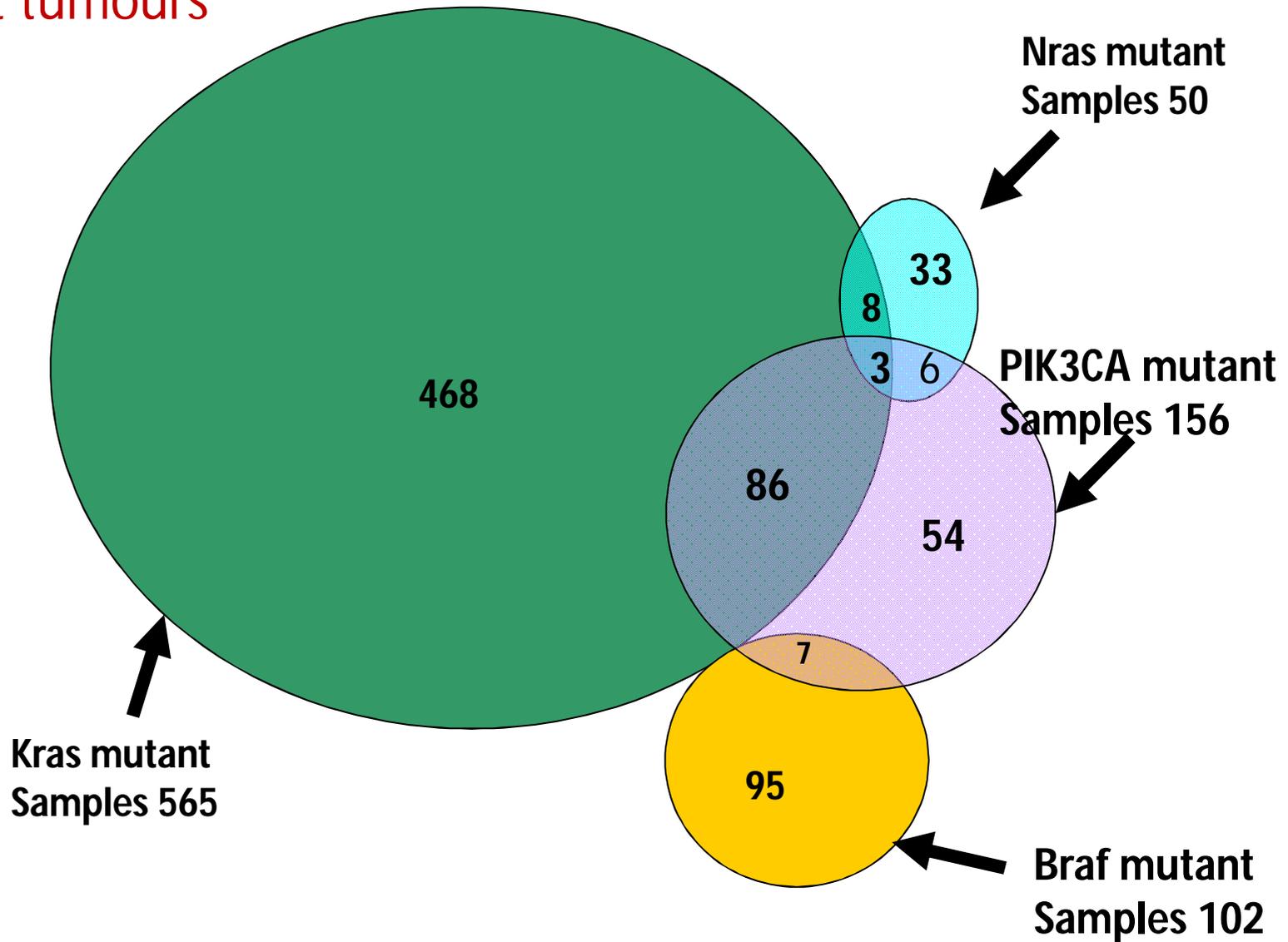
Why conventional designs unsatisfactory

- Some prospective designs aim to evaluate both a new treatment and a biomarker within one trial

    - 'biomarker stratified' design or 'marker by treatment interaction' design

    - inefficient because need to size trial either on the difference between the effect of the treatment in biomarker positive and negative patients (an interaction) or on the effect in all patients, which is likely to be modest

- Adaptive trials have been designed (*e.g.,* I-SPY & BATTLE)

    - but these are for the earliest stages of identifying candidate novel agents (phase 2a)

    - also ignore any prognostic effect of different biomarkers

Lessons from prior colorectal cancer trials COIN & FOCUS 3

- CRC includes some clearly defined molecular subtypes (validated or only partially validated) with differing prognosis and pathway activation
  - mutations in KRAS, NRAS and BRAF define largely non overlapping groups
- Biomarker characterisation is achievable in multicentre trials in the NHS
- Two expert labs working together provides a robust way to provide a national biomarker service in clinical trials
- Large numbers of patients can be enrolled in UK (60-70 / mo)
- Patients and clinicians are very interested in trials which test therapies on the basis of 'personalisation'
- Complex trial designs are acceptable to patients and clinicians

Overlap between KRAS, NRAS, BRAF and PIK3CA mutant tumours

Nras mutant
Samples 50

PIK3CA mutant
Samples 156

Kras mutant
Samples 565

Braf mutant
Samples 102

468

33

8

3   6

86

54

7

95

Not drawn to scale...

What is FOCUS4?

- A molecularly stratified trials programme for patients with advanced or metastatic colorectal cancer

- For patients who are stable or responding to first-line chemotherapy, it takes advantage of the chemo break that patients appreciate and UK clinicians like to employ *before* resistance to standard agents occurs to test the efficacy of novel agents against a placebo
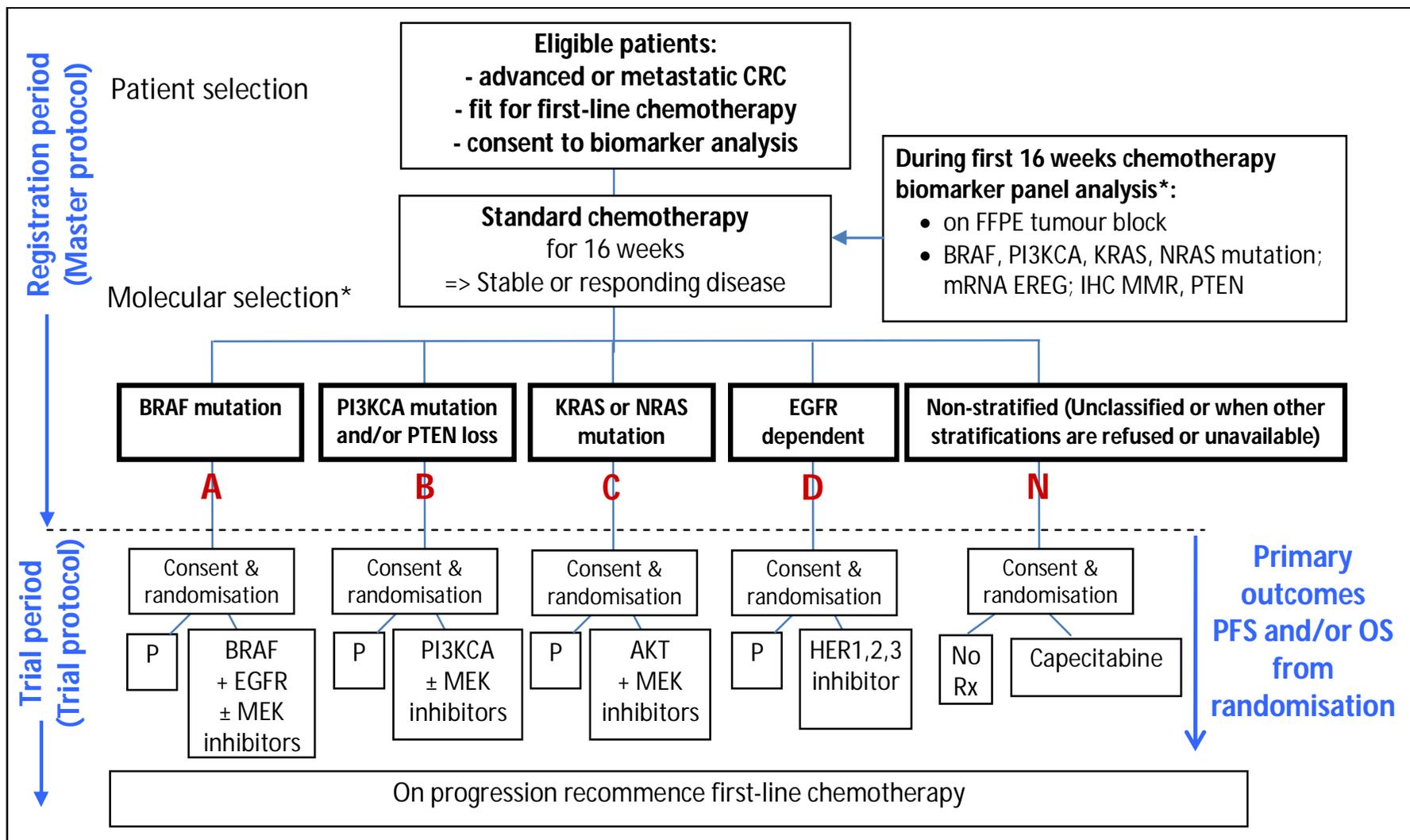
FOCUS4 aims

- To test rationally selected targeted drugs (generally, not tested before in colorectal cancer) 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 with potential for continuing as phase 3 in any or all of the cohorts

Biomarker panel in FOCUS 4

- Somatic mutations
  - KRAS (codons 12, 13, 61, 146), BRAF (V600E), hNRAS (codons 12, 13 & 61), and PIK3CA (codons 9 and 20) using DNA extracted from up to 5 tumour-containing samples

- mRNA
  - EREG, DUSP4 & 6 expression on mRNA extracted from FFPE, analysed in duplicate by QRT-PCR assays and compared with three internal reference genes.
    - to be used for stratification in the all wild type cohort

- Protein (IHC)
  - hMLH-1, MSH-2 or -6 and PMS-2
  - PTEN (Cell Signalling Technology antibody); high throughput sequencing and methylation for PTEN for negative / low expression on IHC.

FOCUS4 schema

FOCUS4 schema flow diagram.

Registration period (Master protocol)

Patient selection

Eligible patients:
- **advanced or metastatic CRC**
- **fit for first-line chemotherapy**
- **consent to biomarker analysis**

During first 16 weeks chemotherapy biomarker panel analysis*:
- on FFPE tumour block
- BRAF, PI3KCA, KRAS, NRAS mutation; mRNA EREG; IHC MMR, PTEN

Standard chemotherapy
for 16 weeks
=> Stable or responding disease

Molecular selection*

| **BRAF mutation** | **PI3KCA mutation and/or PTEN loss** | **KRAS or NRAS mutation** | **EGFR dependent** | **Non-stratified (Unclassified or when other stratifications are refused or unavailable)** |
| A | B | C | D | N |

Trial period (Trial protocol)

| Consent & randomisation | Consent & randomisation | Consent & randomisation | Consent & randomisation | Consent & randomisation |

| P | BRAF + EGFR ± MEK inhibitors | P | PI3KCA ± MEK inhibitors | P | AKT + MEK inhibitors | P | HER1,2,3 inhibitor | No Rx | Capecitabine |

Primary outcomes PFS and/or OS from randomisation

On progression recommence first-line chemotherapy

The molecular cohorts are arranged in a hierarchy from left to right. For example a patient with both a PI3KCA mutation and a KRAS mutation will be classified into the PI3KCA mutation cohort.

Advantageous aspects to FOCUS4

- Uses molecularly enriched cohorts to maximise the possibility of detecting promising new treatments or rejecting unsuccessful ones

- Uses multi-stage trial design with analyses at pre-specified time points for early detection of sufficient activity

- Tests more than one treatment at the same time, each against its own placebo control

- Moves seamlessly from phase 2 to 3

- Tests whether activity is specific to the molecular subgroup

Advantages to F4 design

- Allows for study when biomarkers are incompletely characterised and/or not fully validated

- 'Umbrella' structure allows for efficient inclusion of less common biomarker cohorts

- Primarily phase II in intention (signal seeking)

- But can continue efficiently into phase III

- Efficient design for ascertaining specificity of any positive results in relation to biomarker selection used

- Adaptive: allows for efficient incorporation of new information or drugs into a large open trial

Other advantages of F4 design

- Relatively early disease setting:
  - Avoids concomitant administration of novel agent & chemo, so novel agents can be tested sooner
  - Tests novel agent alone, not in conjunction with known active therapy
- Tests each agent in an 'enriched' population:
  - Biomarker selected
  - Responding (not resistant) to first-line chemo
  - Patients with high baseline platelets excluded (pending validation)
- Nested into large trial framework
  - Many sites / fast recruitment
  - Can be adapted/modified/arms added during trial lifetime
- Multistage design (staged signals & commitment)
- Biomarker cohorts are <u>not</u> compared to each other
- Randomised MAMS design allows all patients to contribute to both phase II and phase III outcomes

FOCUS 4: design considerations

- Each biomarker/treatment comparison has 4 stages

- 2 lack of activity stages, where randomisation can be ceased (phase II)
  - Progression-free survival

- 2 efficacy stages (phase III)
  - Progression-free survival
  - Overall survival

- 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

MAMS design operating characteristics

	Stage I Safety	Stage II Lack of	Stage III Efficacy	Stage IV Effi...
Outcome				
1-sided				
Power				
Target				
Critical	0.91	0.83	0.79	0.80
Time required (months)	20.0	10.6	11.7	18.5
Cumulative time (months)	20.0	30.6	42.3	60.8
Cumulative events required: **Total (control arm)**	**109** **(41)**	**198** **(72)**	**301** **(107)**	**289** **(109)**
Total expected cumulative randomisations	**180**	**275**	**381**	**547**

Target recruitment

Registration of 2400 patients in order to randomise 1536 patients across all trials

Recruitment to commence in 2013 for 4-5 years with additional 2-3 years follow-up

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

How can this all work?

- The structure, influence and guidance of the NCRI
- Government funding
    - National Institute of Health Research / EME
    - Medical Research Council
- Charity funding
    - Cancer Research UK
- A new type of stage-by-stage interaction with funders to confirm the strategic adaptations over the course of the trial
- Commercial partnerships, *eg* AZ, GSK, Pfizer, others
- Infrastructure investment
    - 4 UK National Cancer Research Networks
    - Clinical Trials Units
    - ECMC network
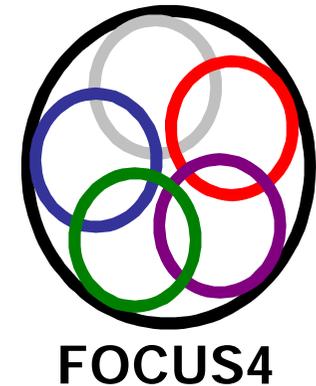- Patients and consumer representatives

FOCUS4 Trial Group

Funding: NIHR/MRC EME and CRUK

Sponsors - MRC CTU
Trial/Data/Project Managers: Cheryl Pugh/Krishna Letchemanan/Anna Bara
Statisticians: Louise Brown, David Fisher, Angela Crook
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Trial Management Group
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                                 Richard Adams (D), Tim Maughan (U)

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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

FOCUS4

Efficacy and Mechanism Evaluation programme

MRC | Medical Research Council

NHS National Institute for Health Research

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