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?

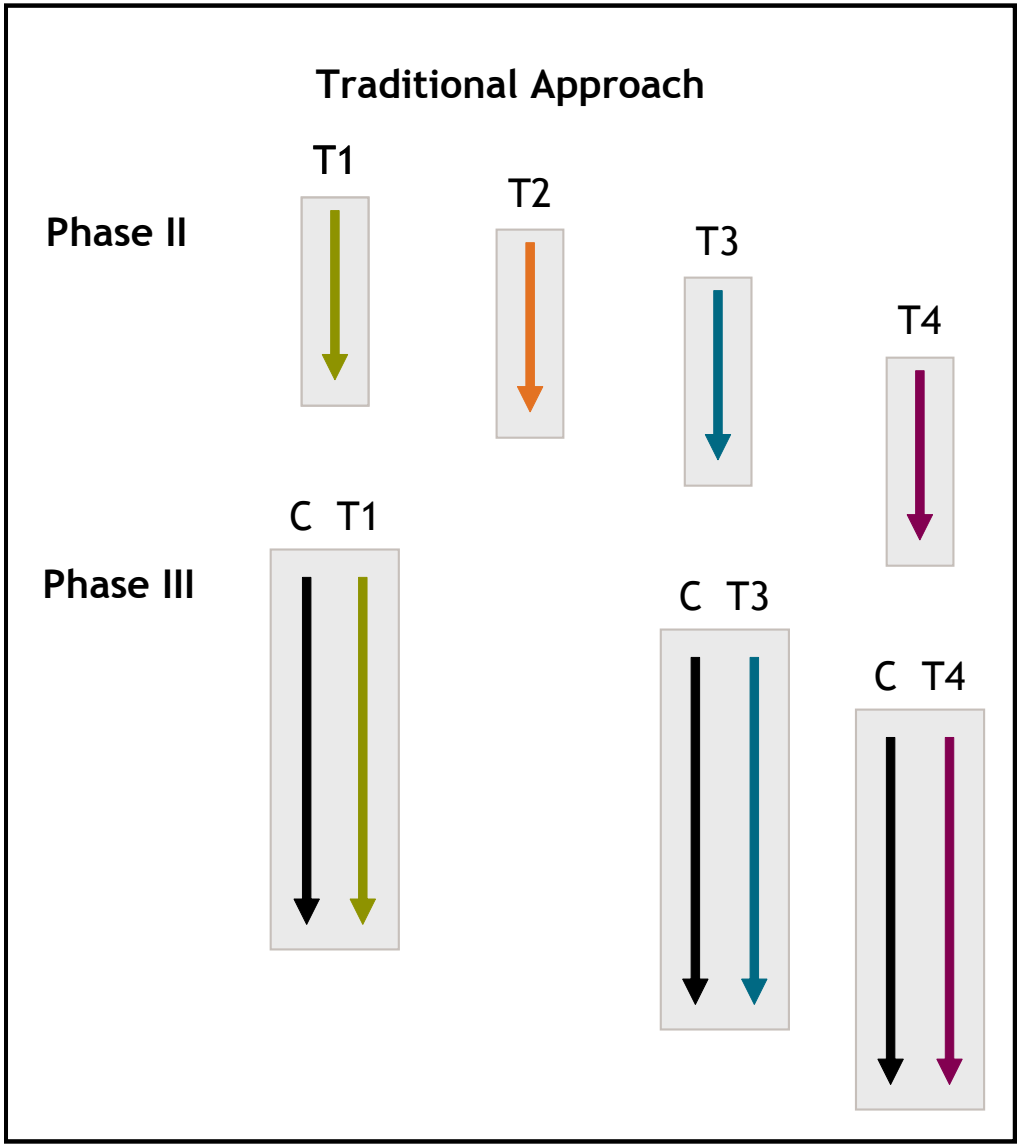
Why we need new trial designs

- 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)

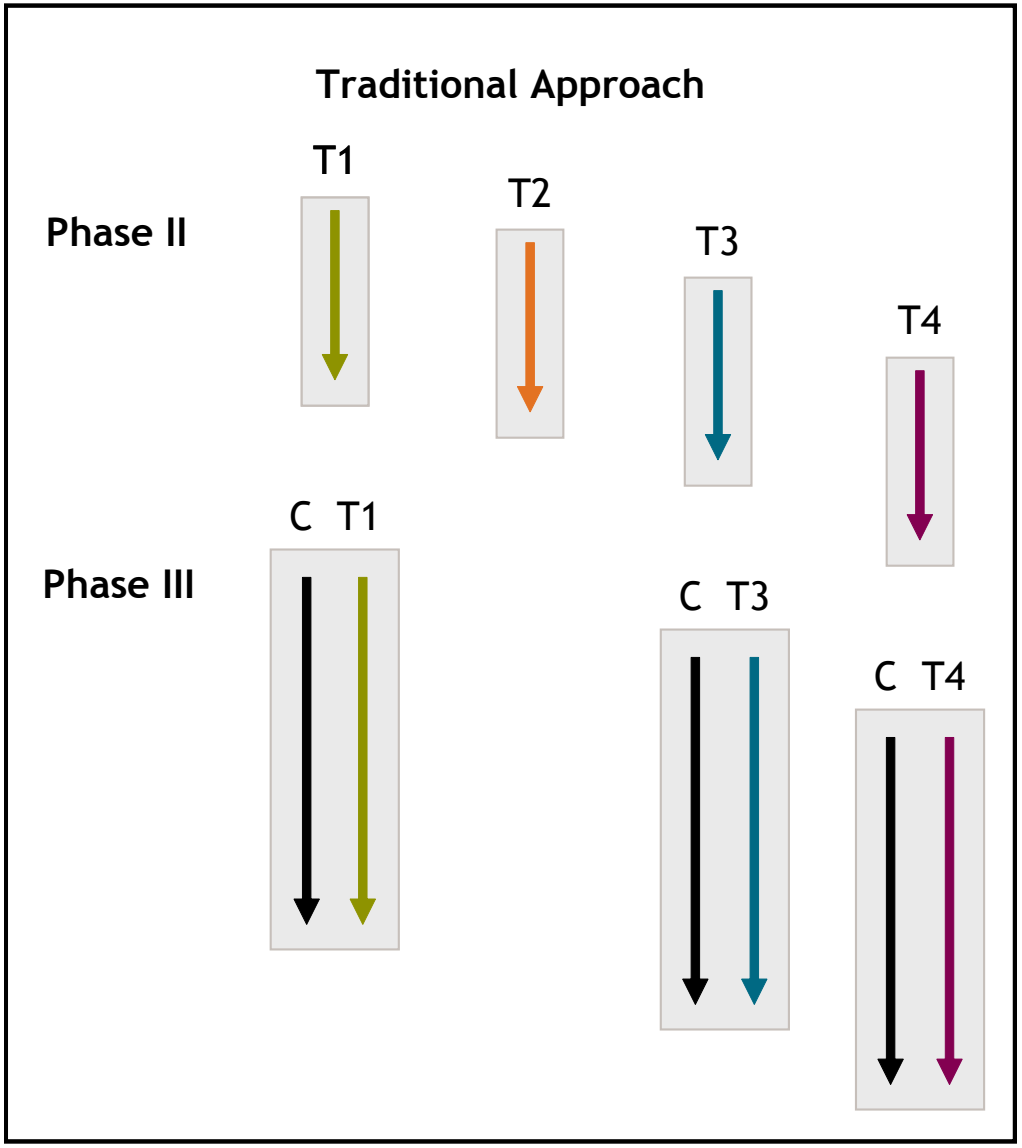
Can we make strategy more efficient?

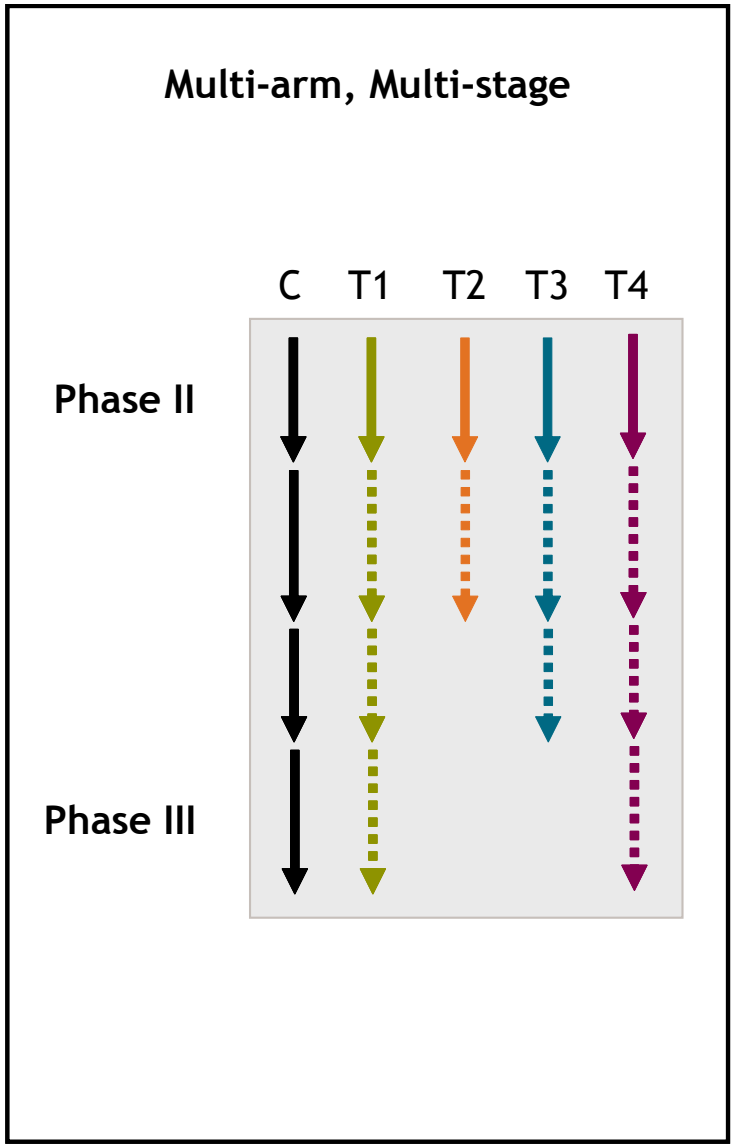
- For initial testing
  - Identify informative clinical settings
    - (regardless of whether a good setting for licensing)
  - Biomarker-enrich
    - (can subsequently expand population and stratify)
  - Seek strong signal of activity
    - (ambitious HR)
- Multi-stage trials
- Multi-arm trials (test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

Traditional approach to testing



Multi-arm multi-stage (MAMS) approach





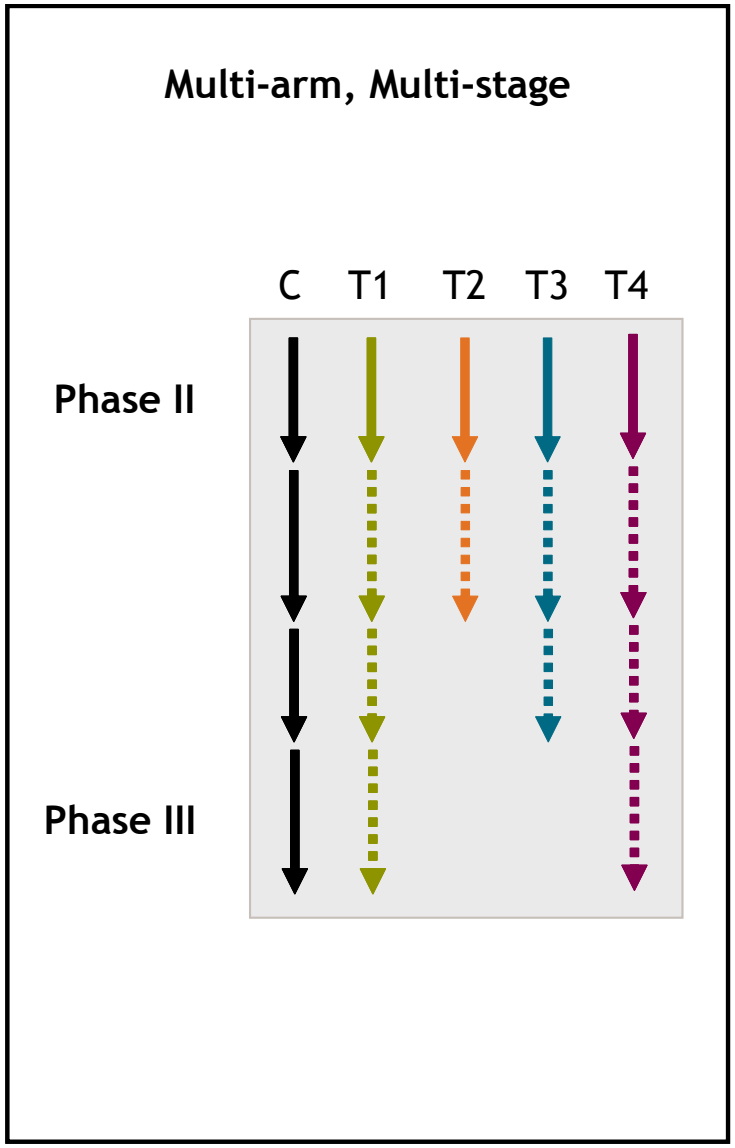
Multi-arm multi-stage (MAMS) approach

Multi-arm

- Test many relevant agents

Multi-stage

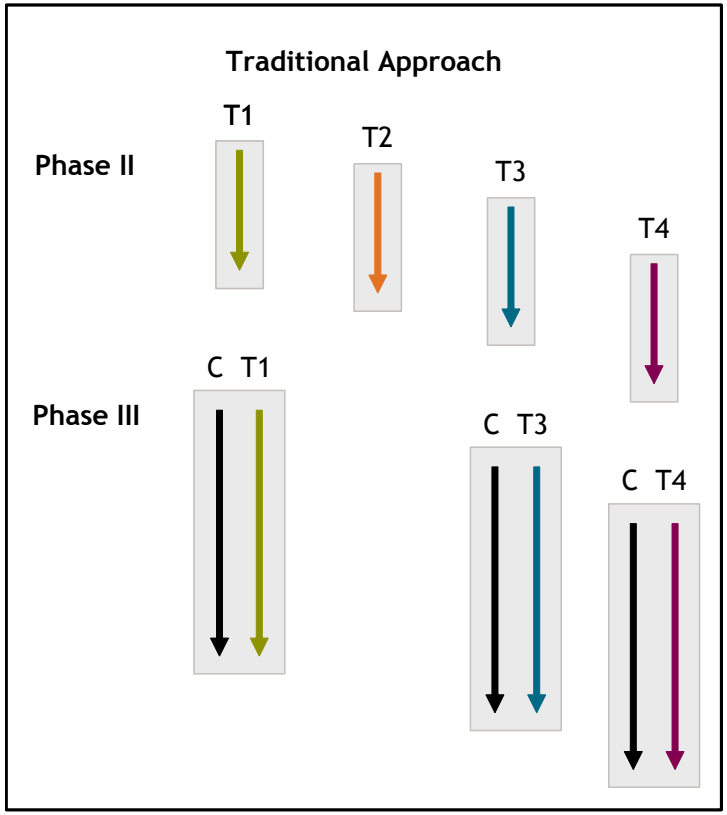
- Ask if reasons to *continue* investigating a treatment?

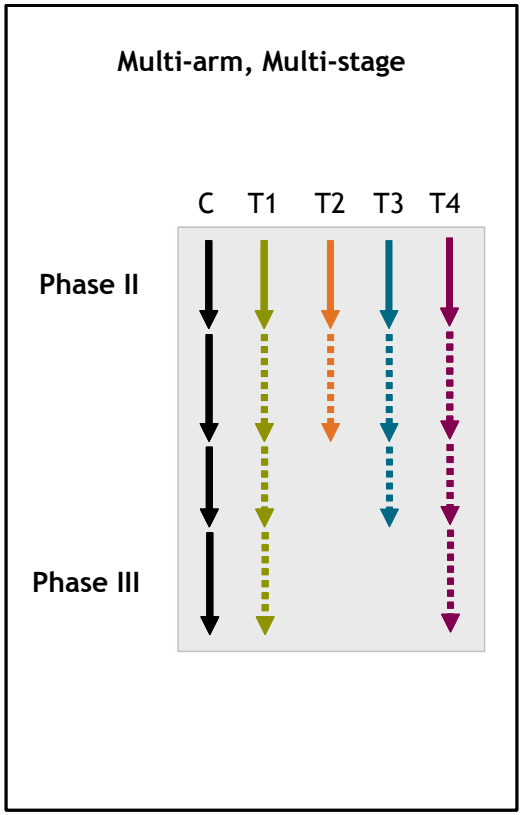


Advantages of MAMS trials

1. Fewer patients
2. Less overall time

- Concurrent assessment of agents
- Randomise from start
- One seamless trial
- One protocol → Less bureaucracy

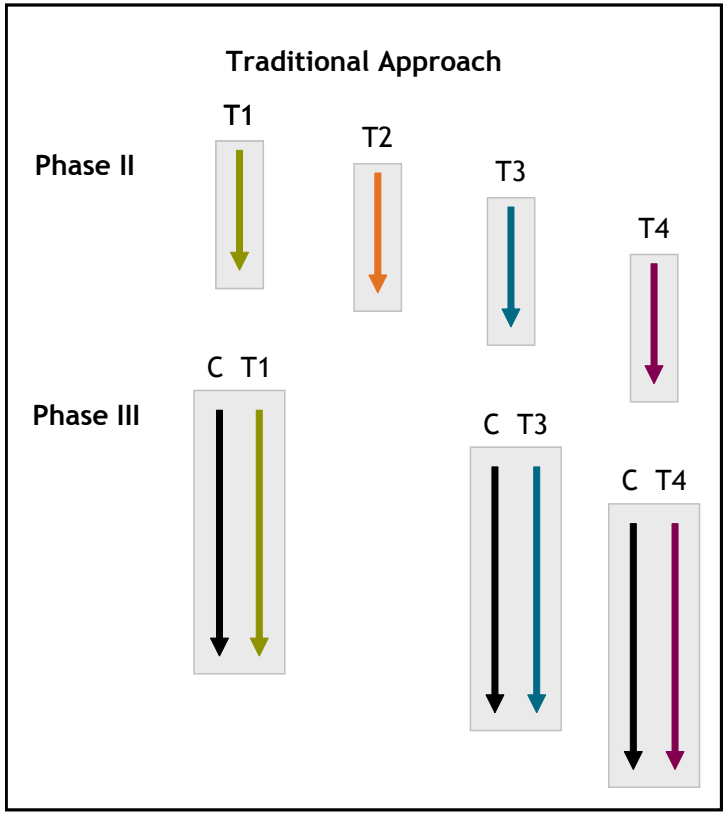


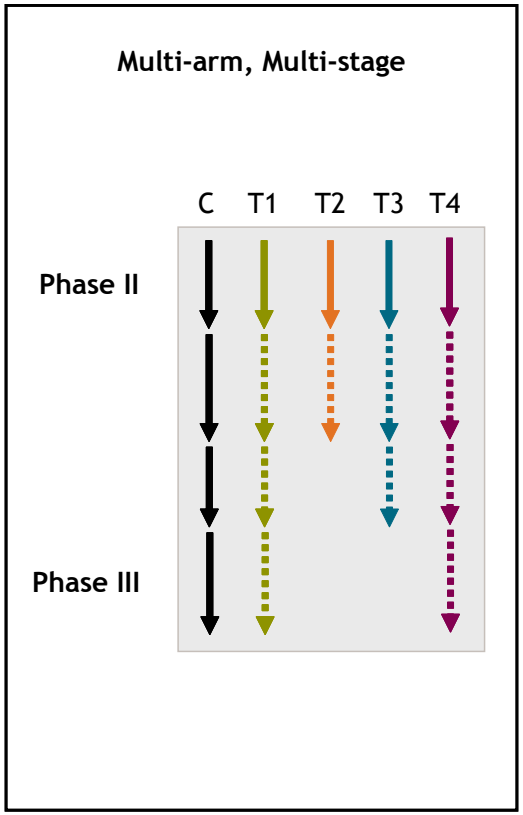


Advantages of MAMS trials

3. Increased flexibility

- Adapts to intermediate results
- Focus on more promising arms

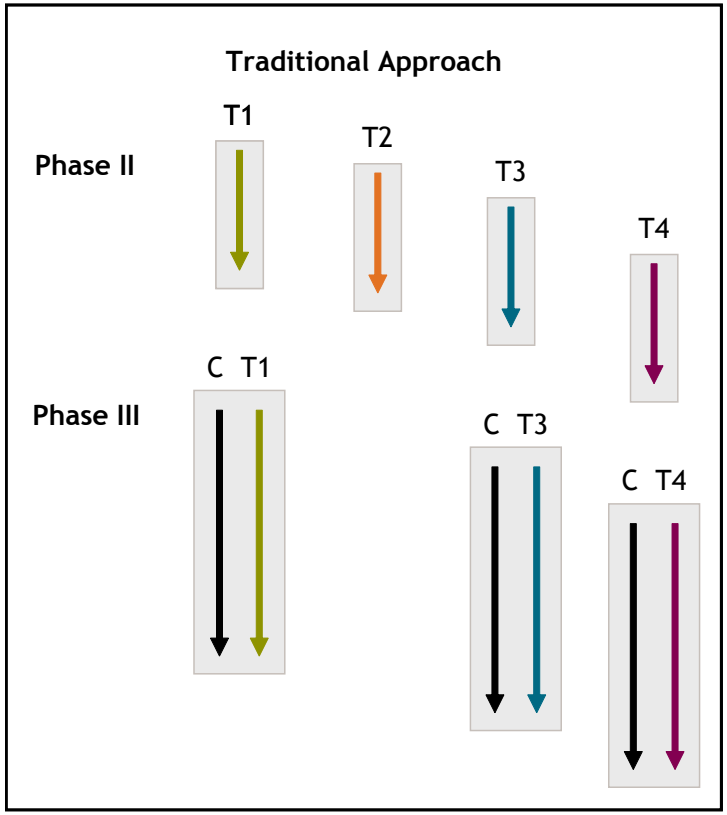


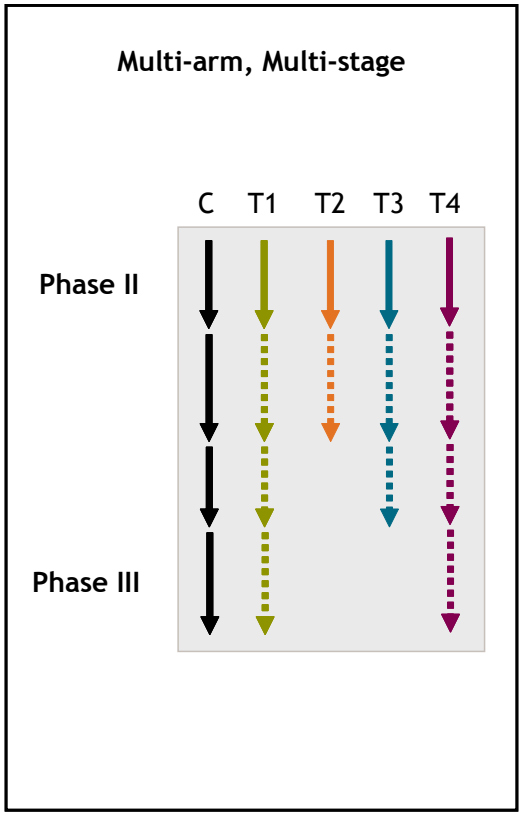


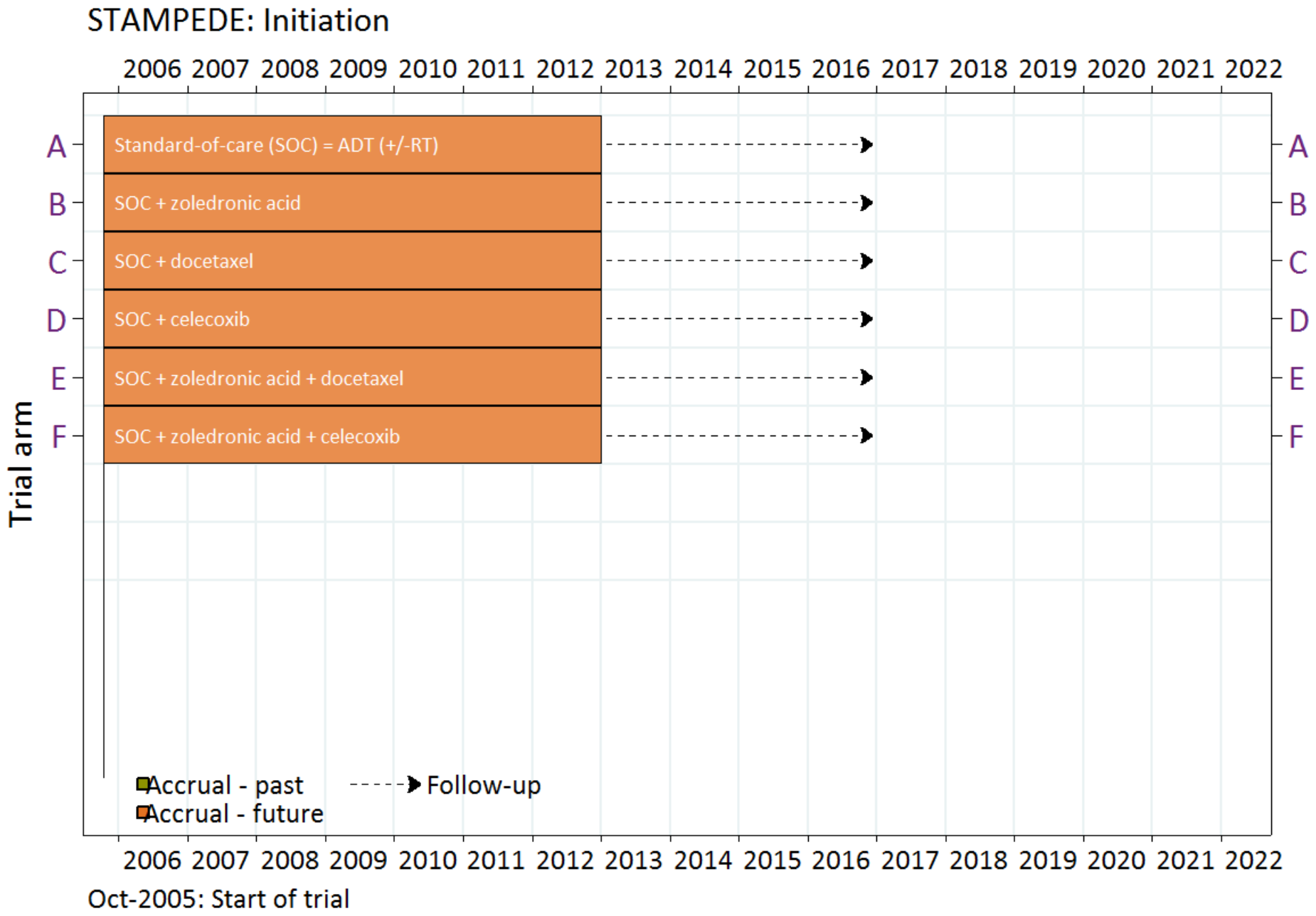
Advantages of MAMS trials

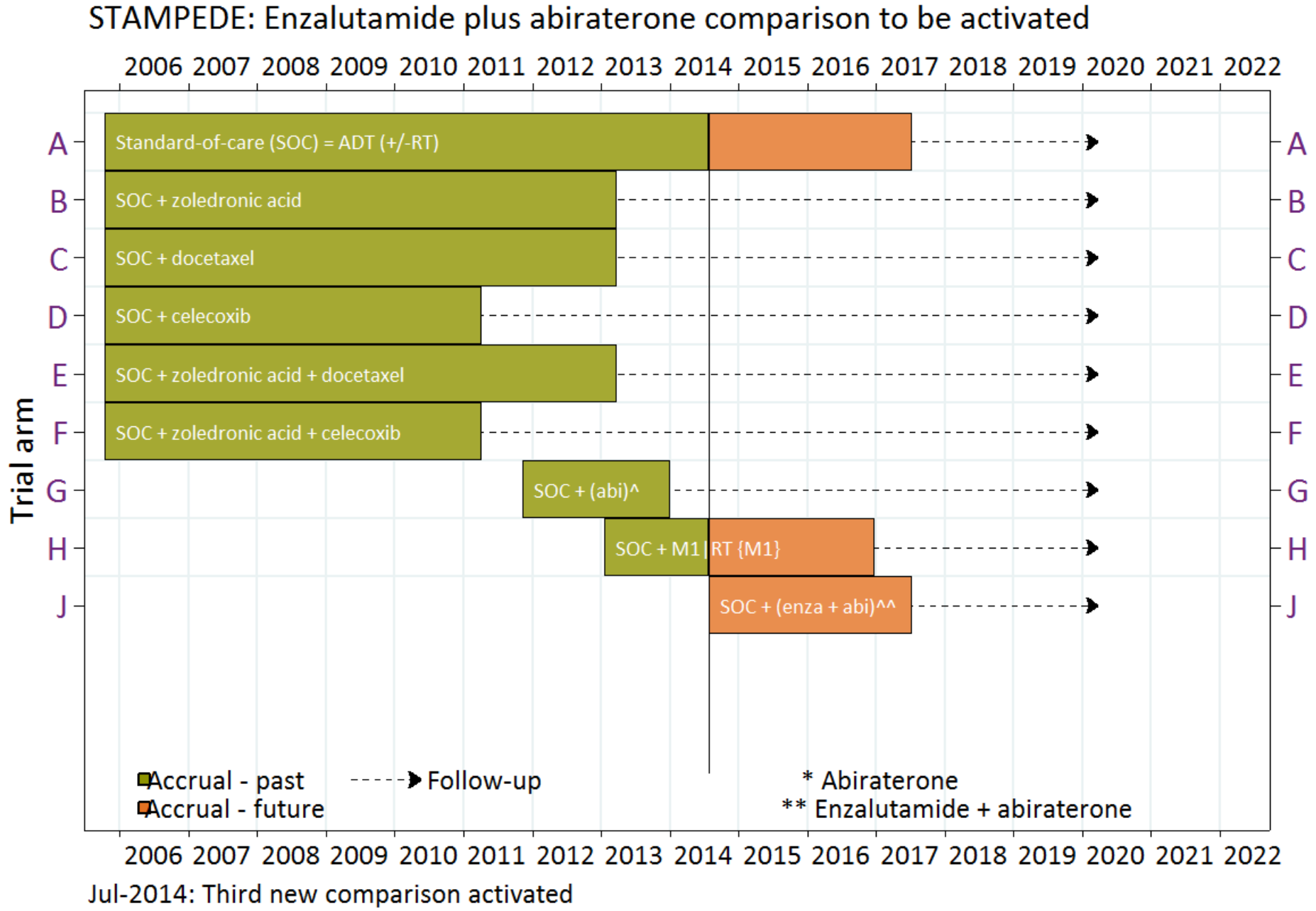
4. Reduced costs

- Limited resources for trials
- Must use fairly and efficiently





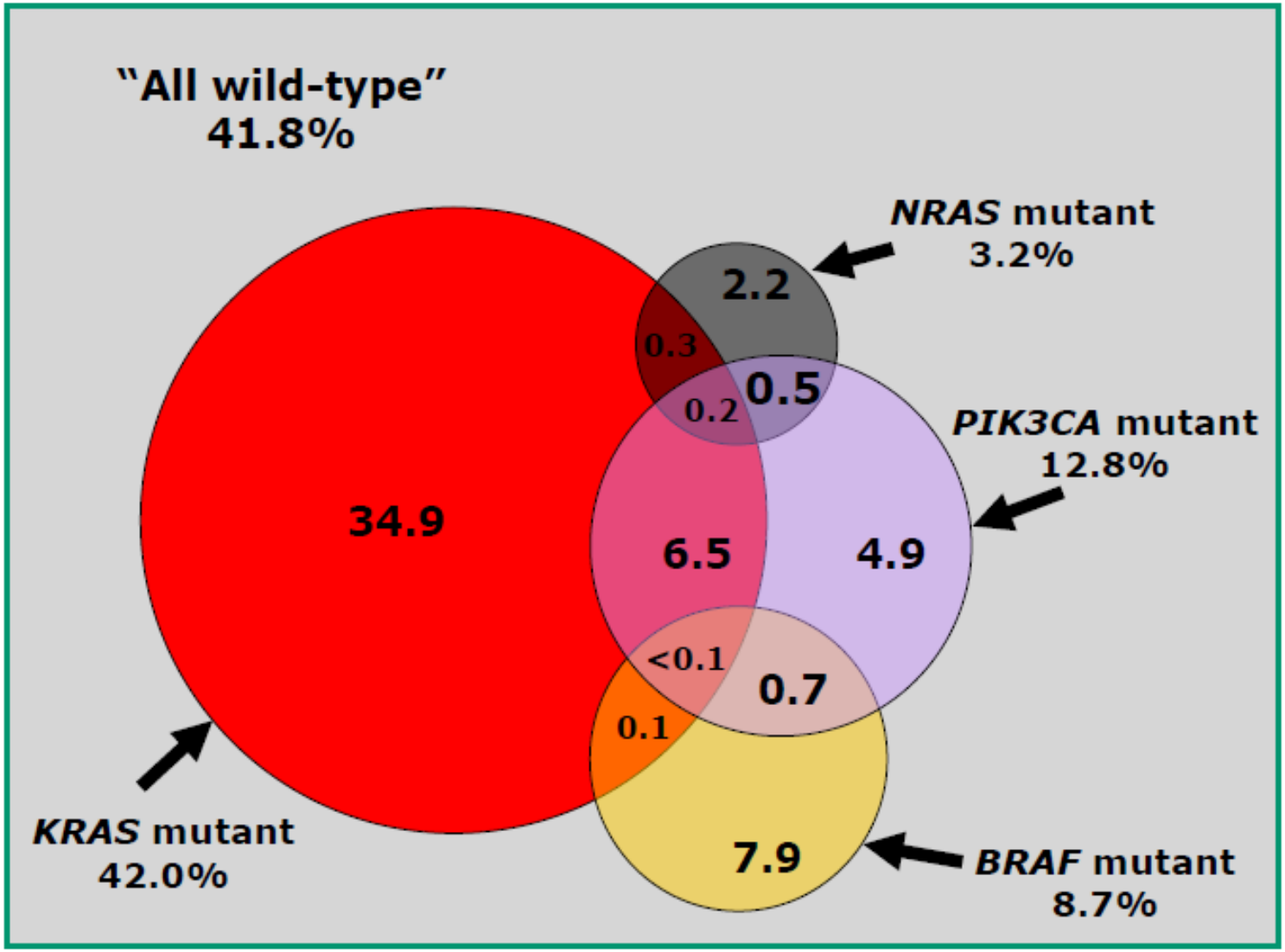

STAMPEDE: Initiation
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Trial arm
A
B
C
D
E
F
Standard-of-care (SOC) = ADT (+/-RT)
SOC + zoledronic acid
SOC + docetaxel
SOC + celecoxib
SOC + zoledronic acid + docetaxel
SOC + zoledronic acid + celecoxib
Accrual - past
Accrual - future
Follow-up
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Oct-2005: Start of trial


STAMPEDE: Enzalutamide plus abiraterone comparison to be activated
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Trial arm
A
B
C
D
E
F
G
H
J
Standard-of-care (SOC) = ADT (+/-RT)
SOC + zoledronic acid
SOC + docetaxel
SOC + celecoxib
SOC + zoledronic acid + docetaxel
SOC + zoledronic acid + celecoxib
SOC + (abi)^
SOC + M1 | RT {M1}
SOC + (enza + abi)^^
Accrual - past
Accrual - future
Follow-up
* Abiraterone
** Enzalutamide + abiraterone
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Jul-2014: Third new comparison activated

CRC Genomic heterogeneity

(Potentially identify biologically & clinically distinct subgroups)

COIN
N=1874



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

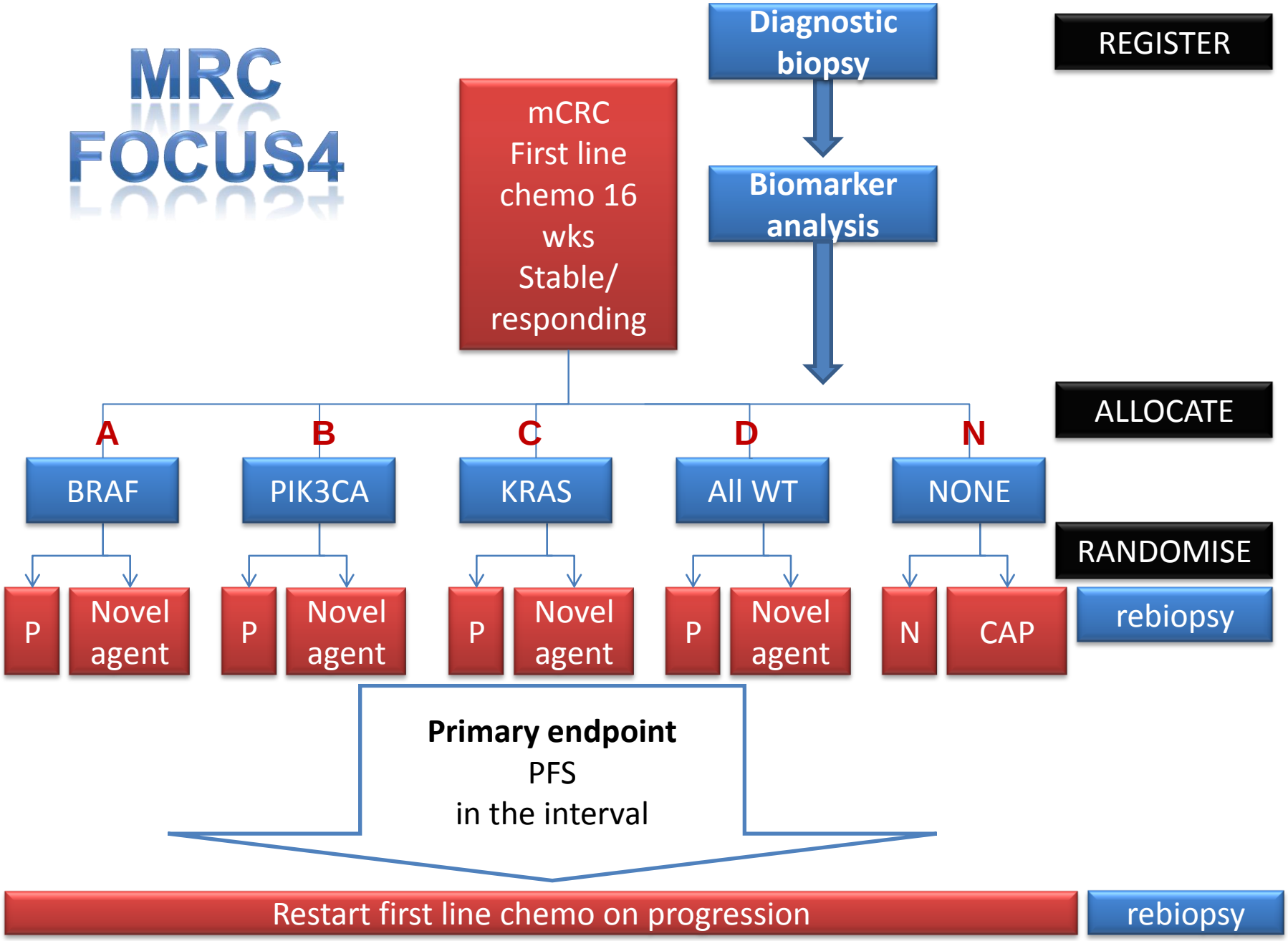
- To test rationally selected targeted drugs for single agent or combined novel-novel activity
  - as demonstrated by an increase in PFS in the chemotherapy-free interval
  - following first line chemotherapy in biomarker enriched subpopulations

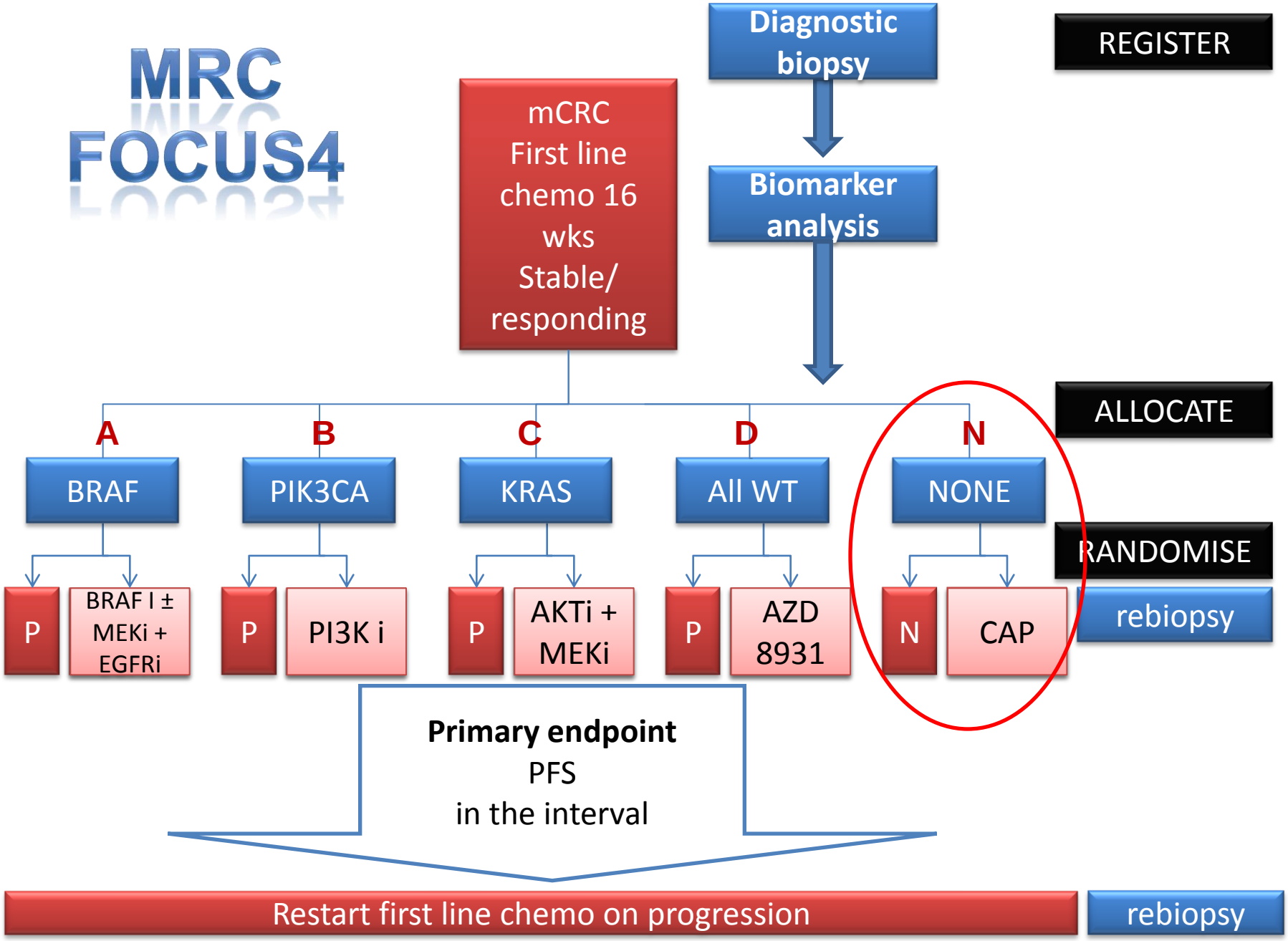
- Phase 2/3 structure: first seeks PFS signal of activity in initial stages; then can continue as a definitive phase 3 trial in any or all of the cohorts, using PFS and OS endpoints

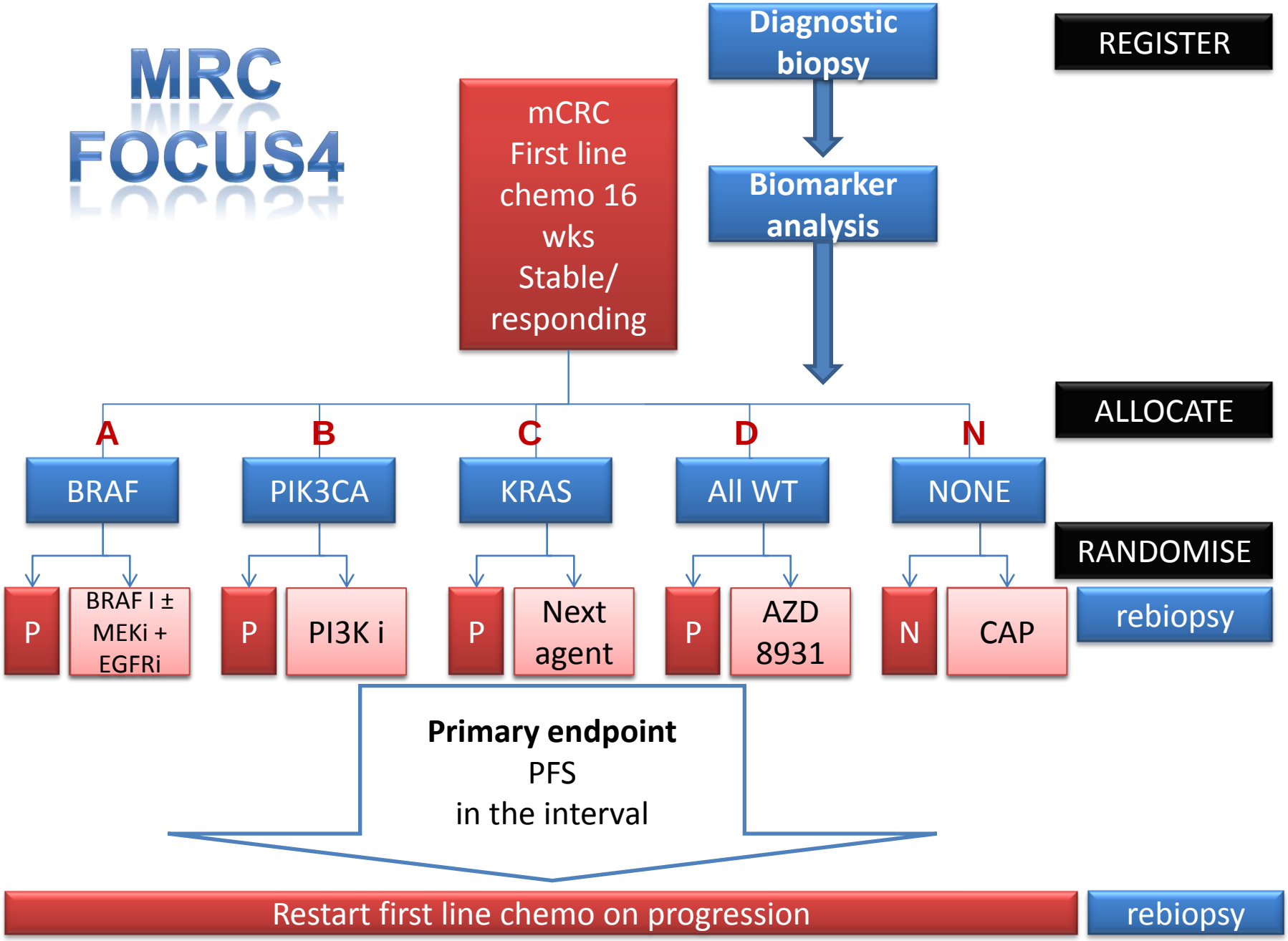
Intermediate endpoints

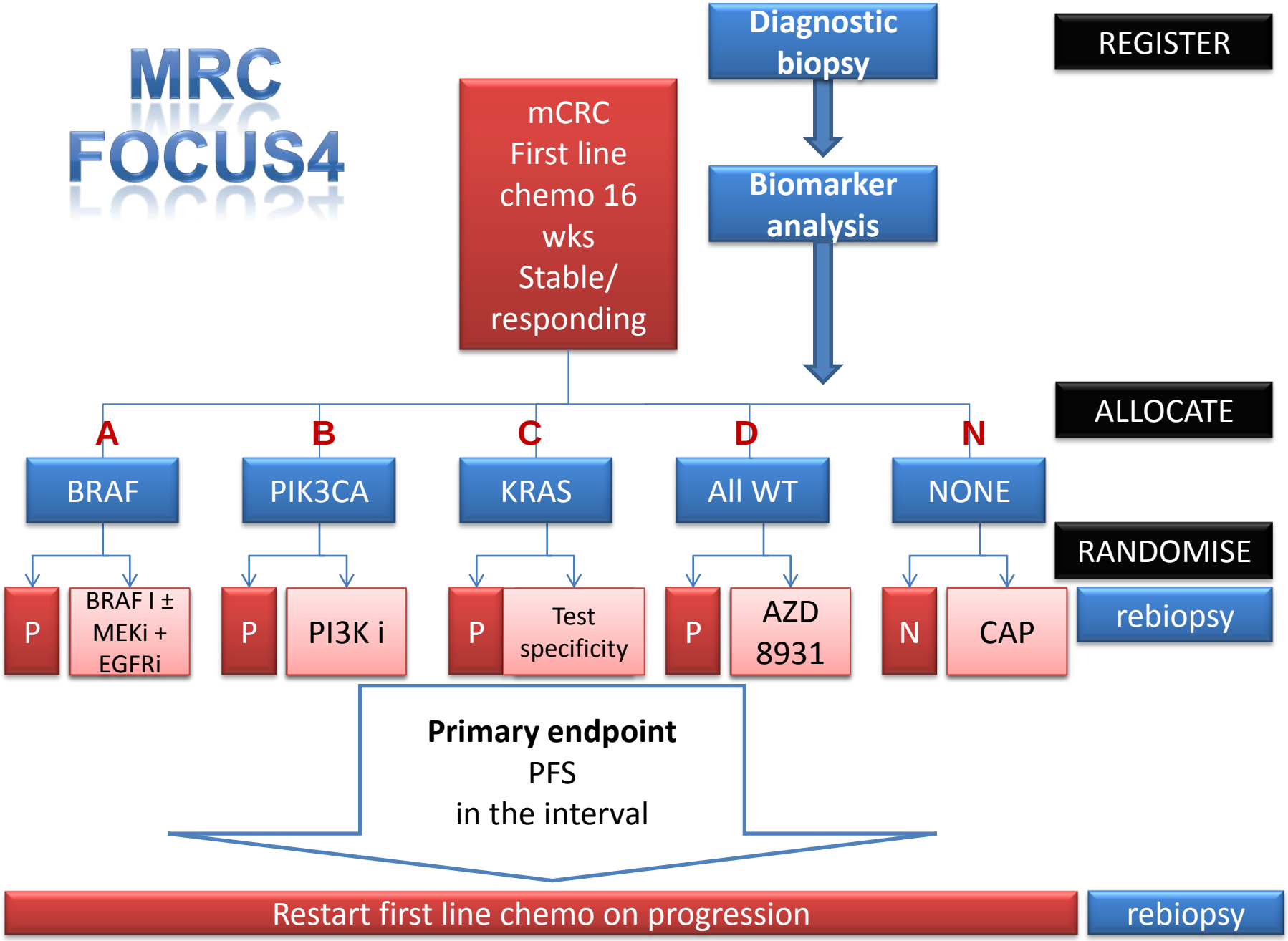
- Use of intermediate endpoints in agent development – for early proof of principle and go/no-go decisions

- ‘Intermediate’ ≠ ‘surrogate’ for registration


MRC FOCUS4
Diagnostic biopsy
REGISTER
mCRC First line chemo 16 wks Stable/ responding
Biomarker analysis
ALLOCATE
A
B
C
D
N
BRAF
PIK3CA
KRAS
All WT
NONE
RANDOMISE
P
Novel agent
P
Novel agent
P
Novel agent
P
Novel agent
N
CAP
rebiopsy
Primary endpoint
PFS
in the interval
Restart first line chemo on progression
rebiopsy


MRC FOCUS4
Diagnostic biopsy
REGISTER
mCRC First line chemo 16 wks Stable/ responding
Biomarker analysis
ALLOCATE
A
B
C
D
N
BRAF
PIK3CA
KRAS
All WT
NONE
RANDOMISE
P
BRAF I ± MEKi + EGFRi
P
PI3K i
P
AKTi + MEKi
P
AZD 8931
N
CAP
rebiopsy
Primary endpoint
PFS
in the interval
Restart first line chemo on progression
rebiopsy


MRC FOCUS4
Diagnostic biopsy
REGISTER
mCRC First line chemo 16 wks Stable/ responding
Biomarker analysis
ALLOCATE
A
B
C
D
N
BRAF
PIK3CA
KRAS
All WT
NONE
RANDOMISE
P
BRAF I ± MEKi + EGFRi
P
PI3K i
P
Next agent
P
AZD 8931
N
CAP
rebiopsy
Primary endpoint
PFS
in the interval
Restart first line chemo on progression
rebiopsy


MRC FOCUS4
Diagnostic biopsy
REGISTER
mCRC First line chemo 16 wks Stable/ responding
Biomarker analysis
ALLOCATE
A
B
C
D
N
BRAF
PIK3CA
KRAS
All WT
NONE
RANDOMISE
P
BRAF I ± MEKi + EGFRi
P
PI3K i
P
Test specificity
P
AZD 8931
N
CAP
rebiopsy
Primary endpoint
PFS
in the interval
Restart first line chemo on progression
rebiopsy

FOCUS 4: design considerations

Each biomarker/treatment comparison has 4 stages:

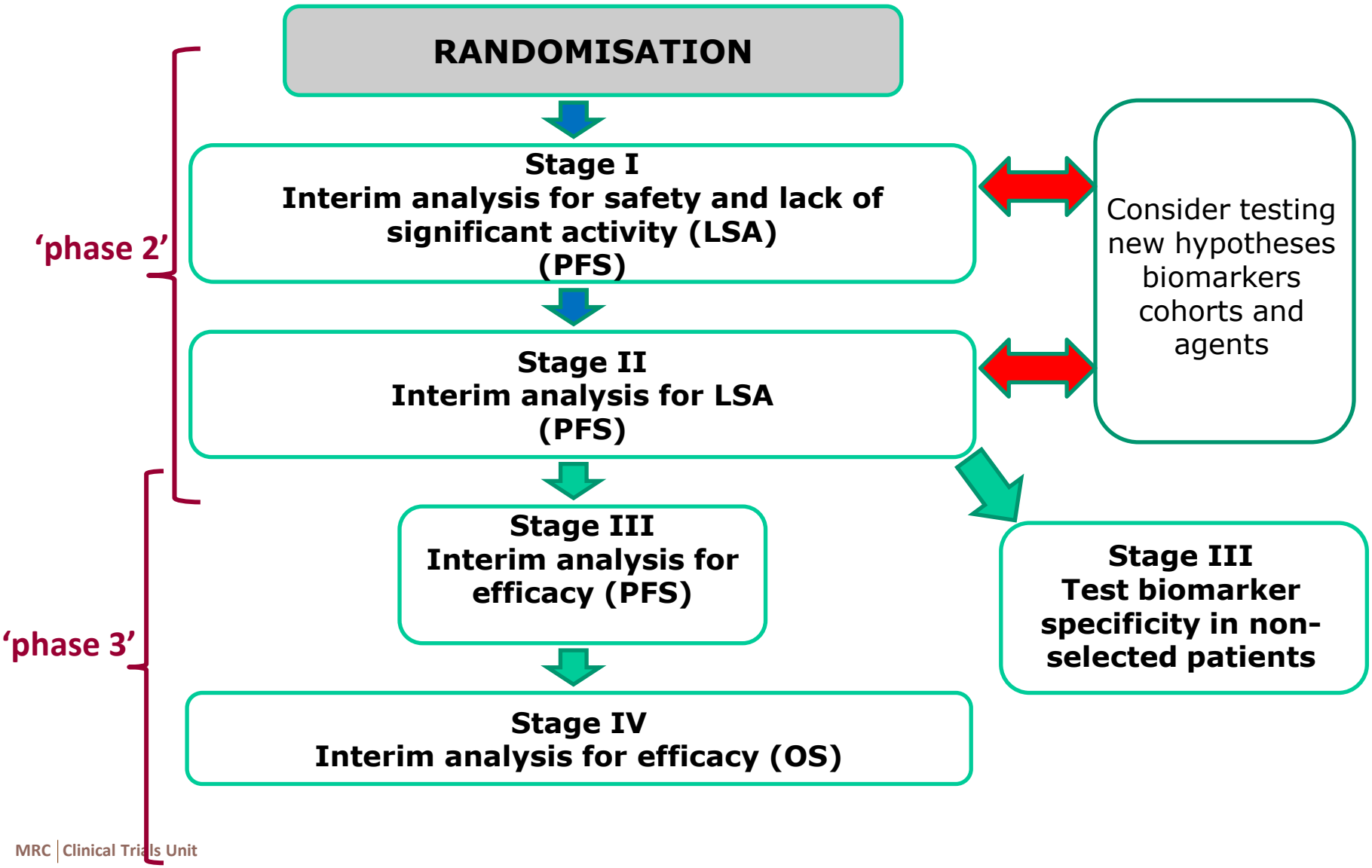
- 2 lack of activity/signal-seeking stages, where randomisation can be ceased (phase II, PFS endpoint)
- 2 efficacy stages (phase III, with PFS and OS endpoints)

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



Projected patient accrual per stage

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

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

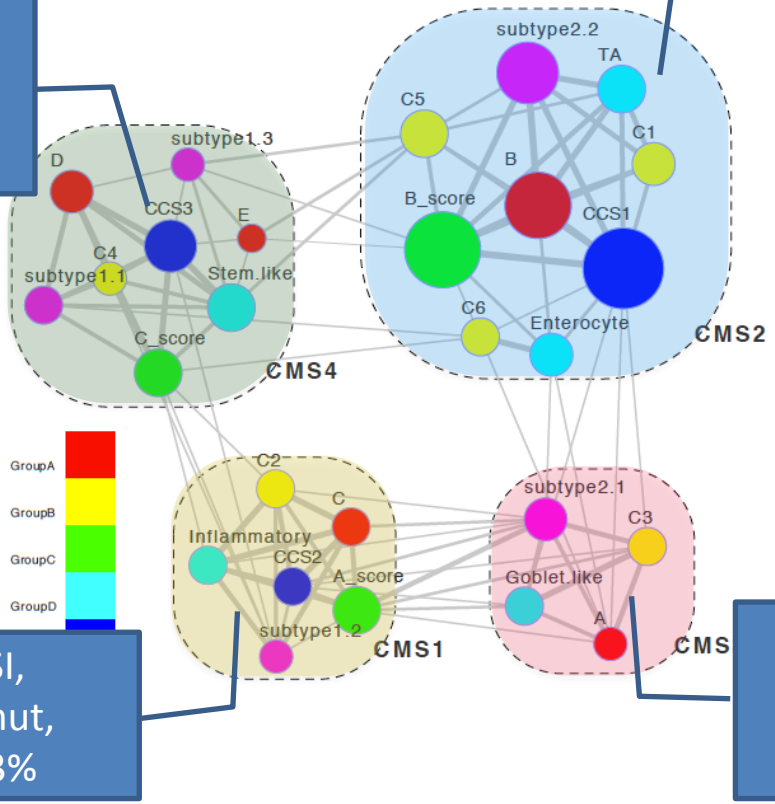
Understanding disease biology

Colorectal Cancer Subtyping Consortium > 4000 cases

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

CMS 2: Epithelial, MSS, high CIN, *TP53* mut, WNT/MYC pathway activation: left colon 35%

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



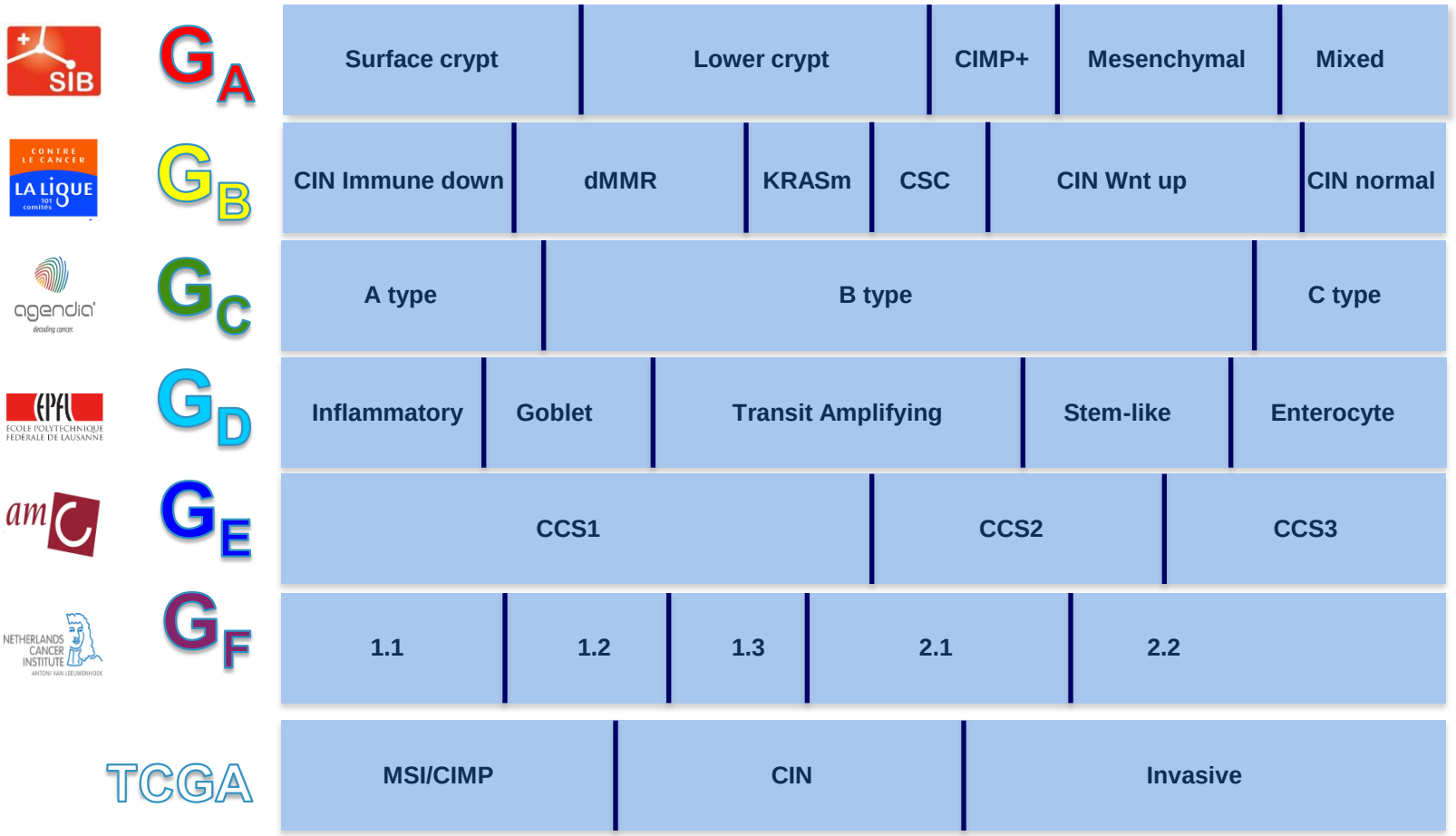
CMS1 Right colon, MSI, hypermutation, *BRAF* mut, immune activation 13%

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

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

Dienstmann R, Guinney J, Delorenzi M, De Reynies A, Roepman P, Sadanandam A, et al. Colorectal Cancer Subtyping Consortium (CRCSC) identification of a consensus of molecular subtypes. ASCO Meeting Abstracts. 2014 June 11, 2014;32(15_suppl):3511

CRCSC – Individual groups' subtypes



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

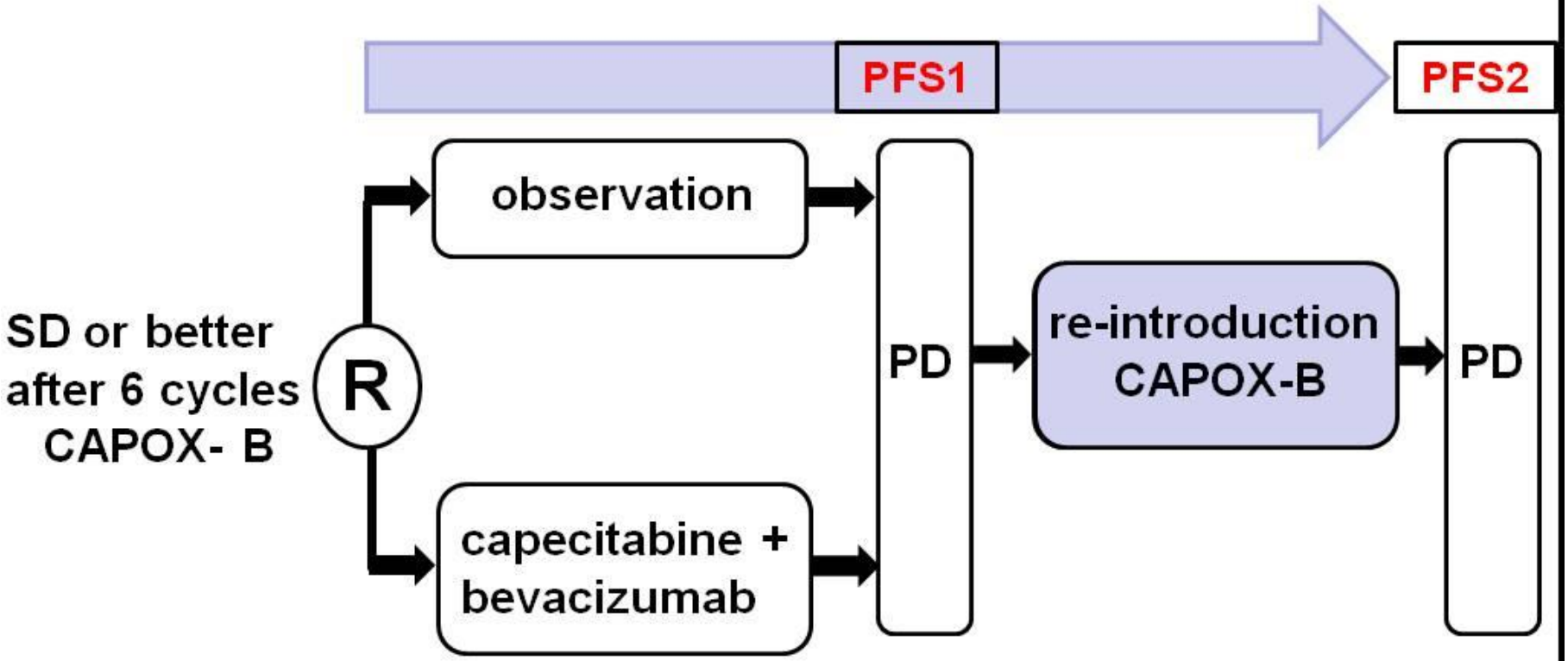
- Assume same target HR for these comparisons as previously; HR=0.5 for PFS (stages 1 to 3) and HR=0.65 for OS (stage 4)

Lesson 3

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

Maintenance, time out and the CDF

Study design



- 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

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