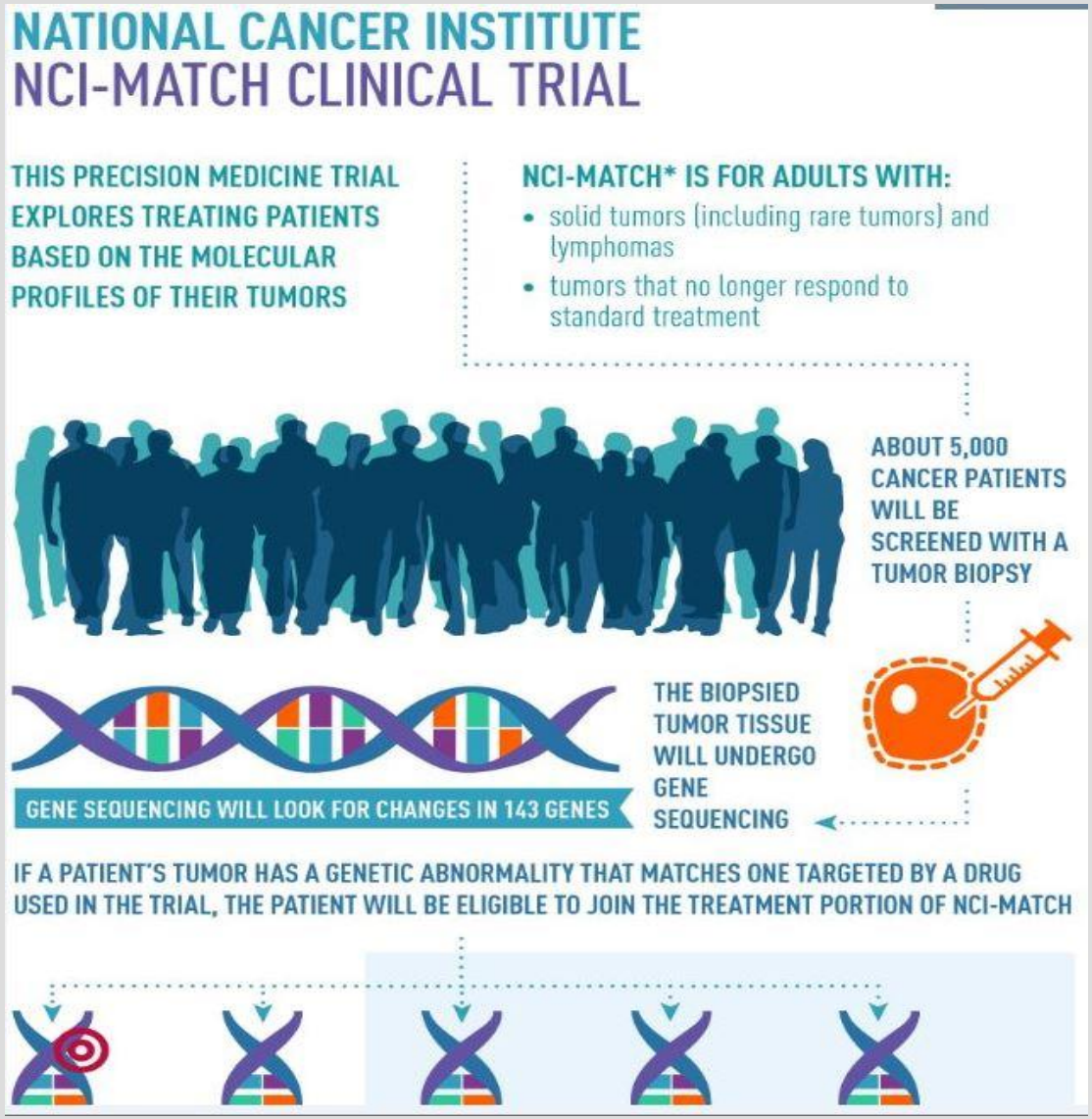
Single arm trials in the context (era) of platforms

R Kaplan

MRC Clinical Trials Unit at UCL

NCI-MATCH trial



NCI-MATCH Expanding to 24 Arms in Late May 2016

Arm / Target	Drugs(s)
A EGFR mut	Afatinib
B HER2 mut	Afatinib
C1 MET amp	Crizotinib*
C2 MET ex 14 sk	Crizotinib*
E EGFR T790M	AZD9291
F ALK transloc	Crizotinib
G ROS1 transloc	Crizotinib
H BRAF V600	Dabrafenib+trametinib
I PIK3CA mut	Taselisib
N PTEN mut	GSK2636771
P PTEN loss	GSK2636771
Q HER 2 amp	Ado-trastuzumab emtansine

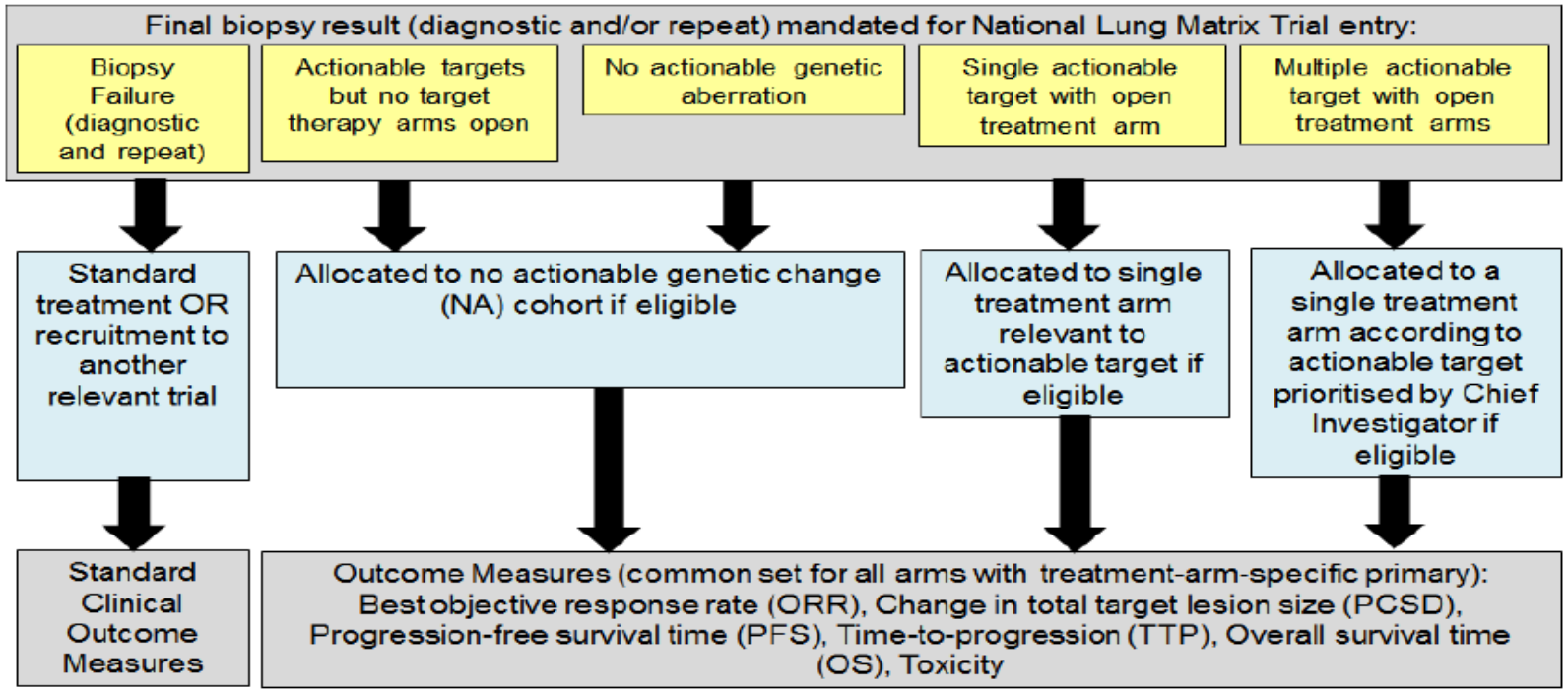
Arm / Target	Drug(s)
R BRAF nonV600	Trametinib
S1 NF1 mut	Trametinib
S2 GNAQ/GNA11	Trametinib
T SMO/PTCH1	Vismodegib
U NF2 loss	Defactinib
V cKIT mut	Sunitinib
W FGFR1/2/3	AZD 4547*
X DDR2 mut	Dasatinib
Y AKT1 mut	AZD 5363*
Z1A NRAS mut	Binimetinib*
Z1B CCND1,2,3 amp	Palbociclib*
Z1D dMMR	Nivolumab*

*Pending approval

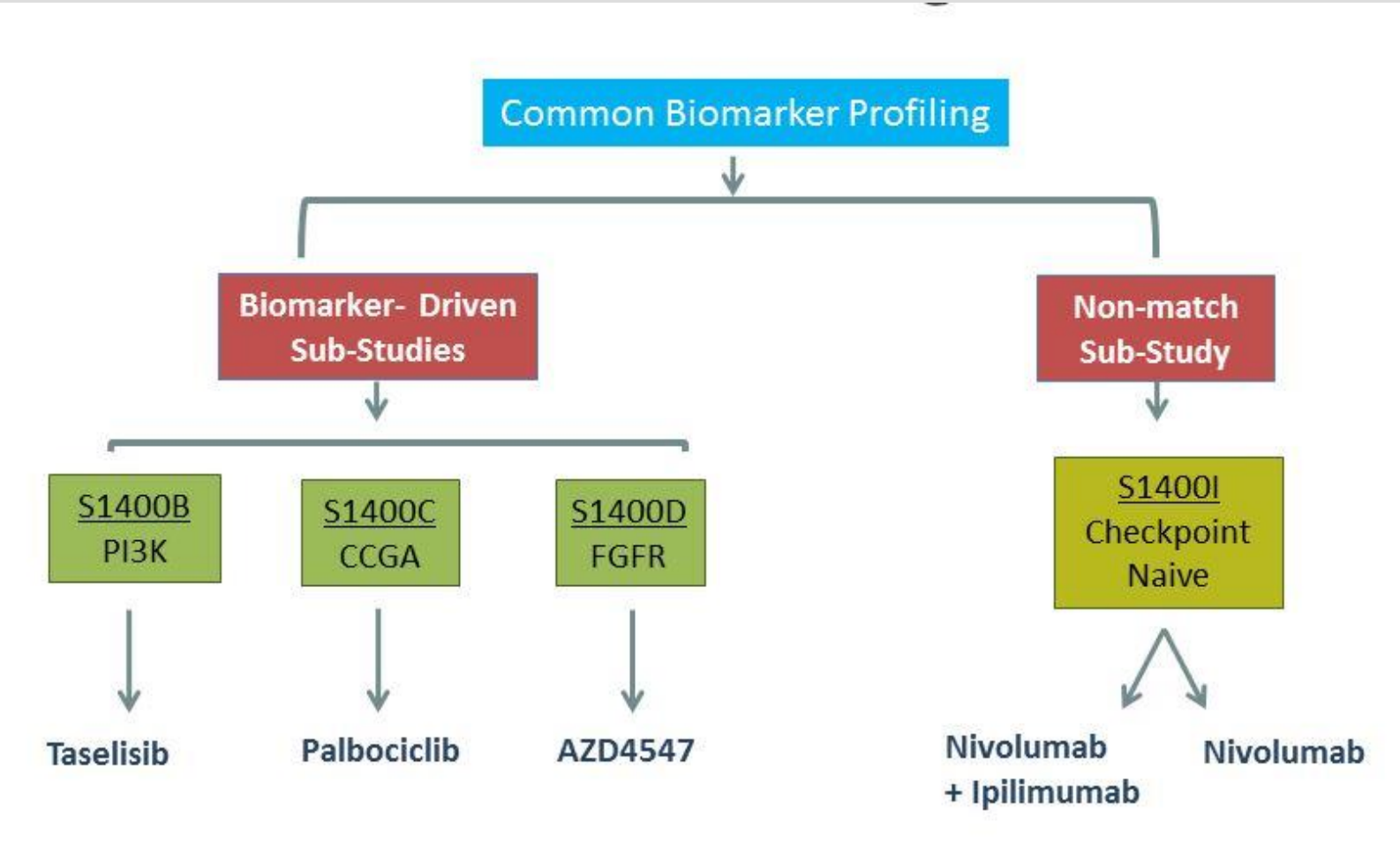
Lung MATRIX trial

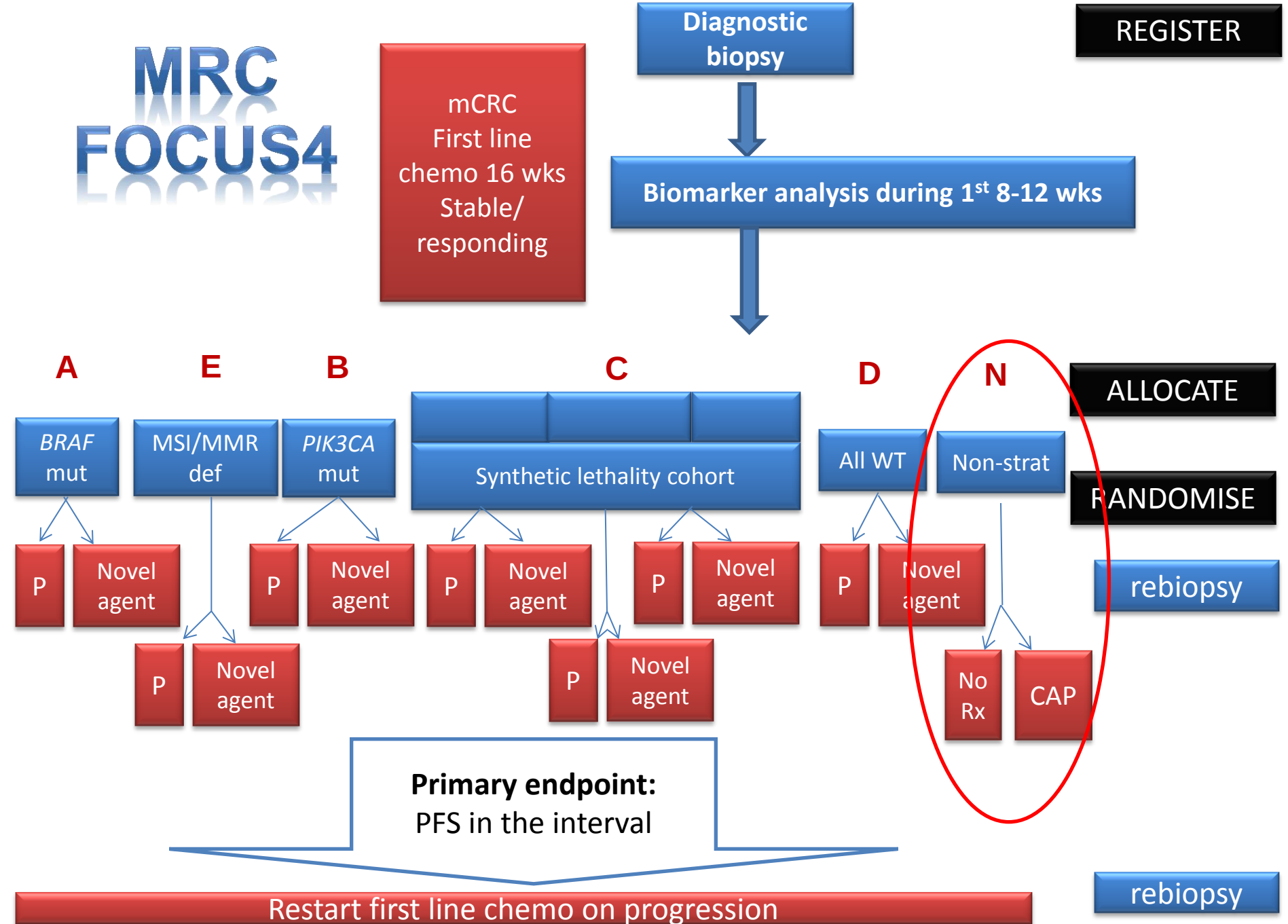
Figure 2: National Lung Matrix Trial Schema

Trial Schema



Lung Map trial




MRC FOCUS4
mCRC First line chemo 16 wks Stable/ responding
Diagnostic biopsy
REGISTER
Biomarker analysis during 1st 8-12 wks
A
E
B
C
D
N
ALLOCATE
BRAF mut
MSI/MMR def
PIK3CA mut
Synthetic lethality cohort
All WT
Non-strat
RANDOMISE
P
Novel agent
No Rx
CAP
rebiopsy
Primary endpoint:
PFS in the interval
Restart first line chemo on progression
rebiopsy

How useful is Objective Response?

- May help in dose/schedule selection
- Objective response remains a useful early readout that is helpful to developers and exciting to patients, media and investors
- RECIST complexity, pseudoprogression . . .
- Waterfall plots reveal some responses in control arms, even placebo arms, of some RCTs
- Objective responses to combinations are a minefield
- Proof of benefit almost always requires associated solid TTE (or duration) endpoints

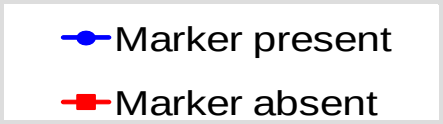
Drawbacks of single arm design

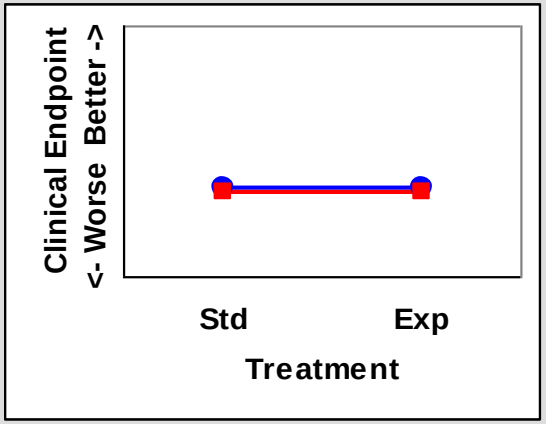
- Implicit comparison with historical data may no longer be valid in the stratified medicine era
- Impact of pre-Rx parameters usually greater than the impact of the treatment
- *May* be able to minimise by extensive characterisation, including of historical controls

- For many agents, and settings, OR or duration is not going to be all that's needed
- May provide a 'Go' but perhaps not a reliable 'No-go'

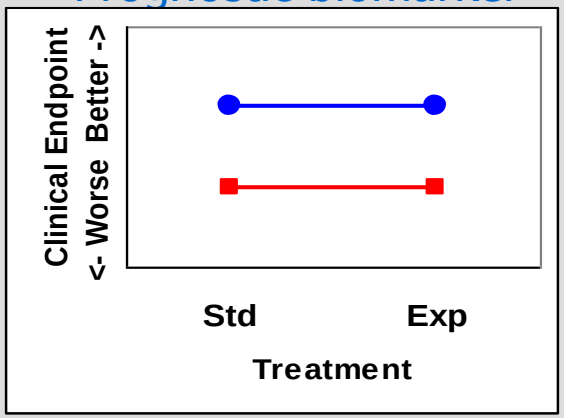
Drawbacks of single arm design

- Biomarker enrichment may not be definitive
- Can't separate prognostic from predictive effects

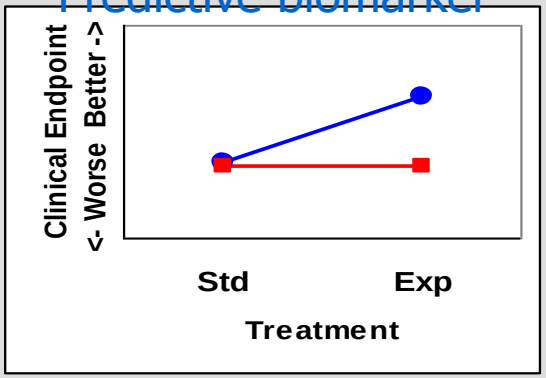




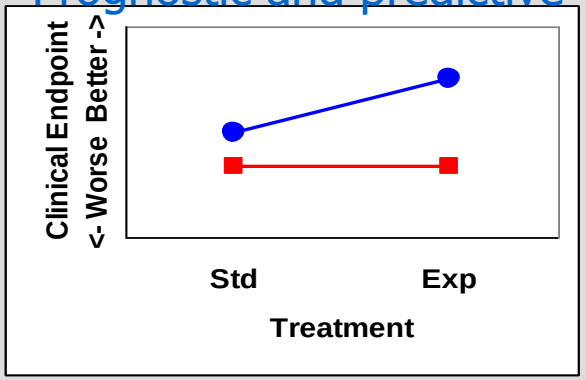
Prognostic biomarker



Predictive biomarker



Prognostic and predictive

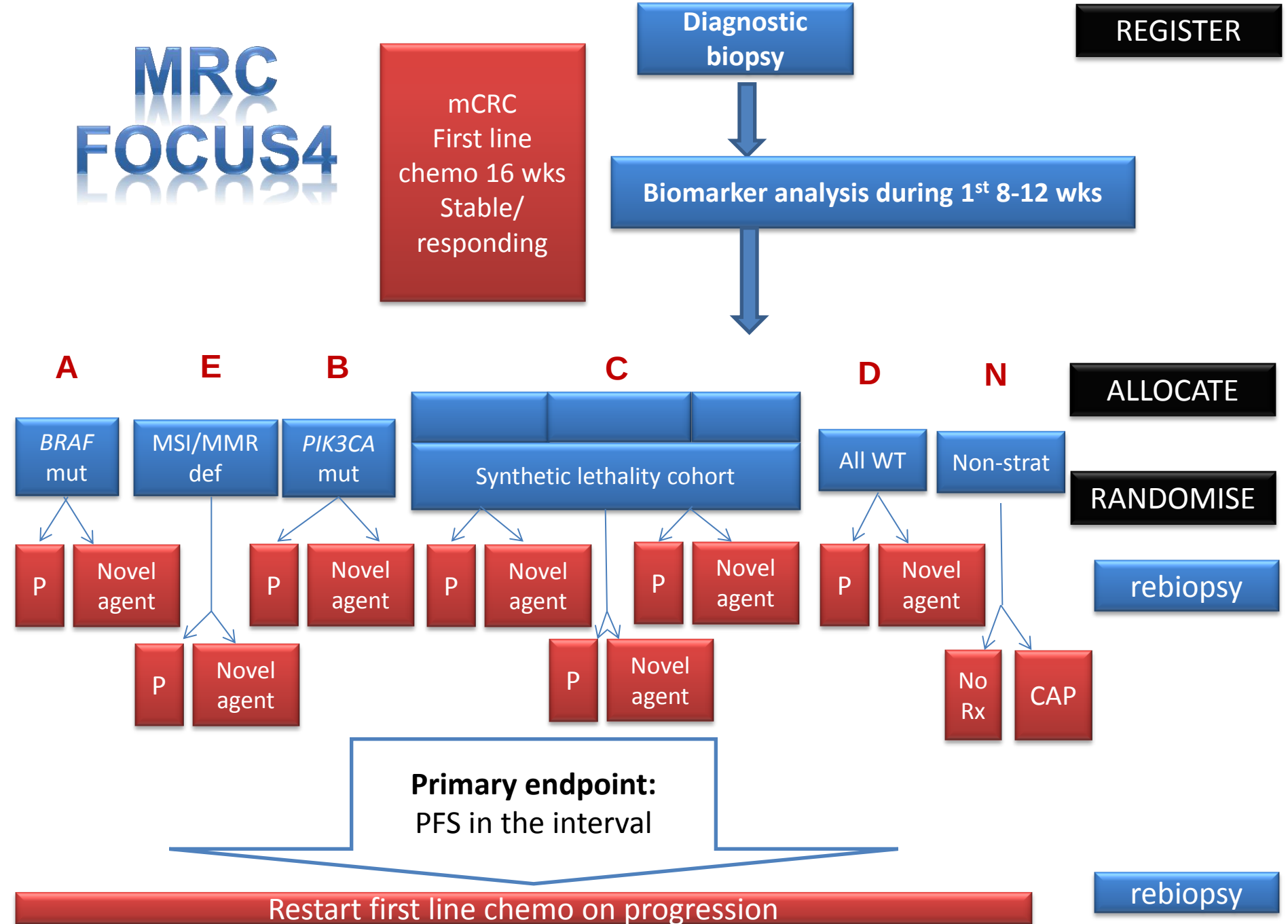


Dan Sargent's group: modelling

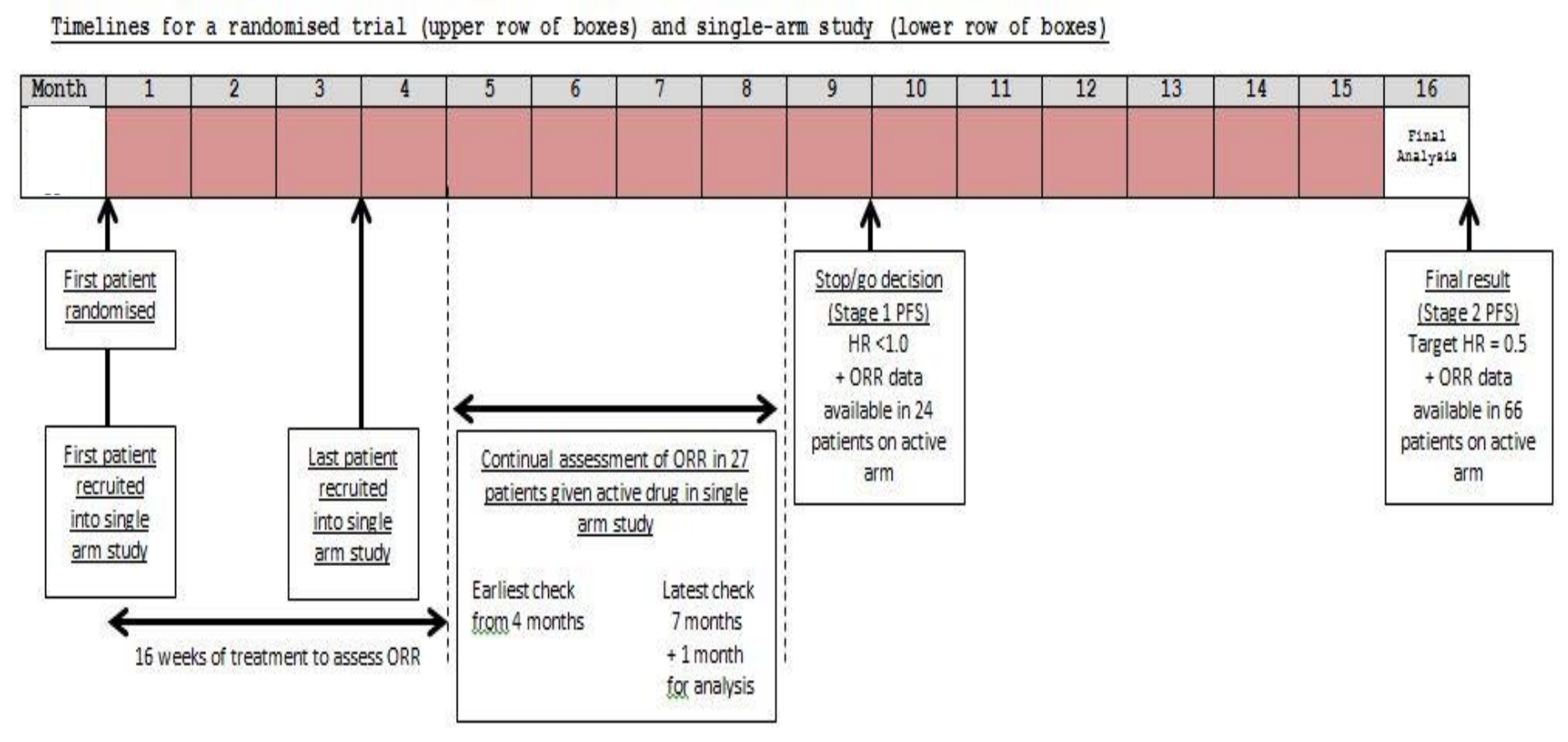
- Variability in historical control success rates, outcome drifts in patient populations over time, and/or patient selection effects can result in inaccurate false-positive and false-negative error rates in single-arm designs
- False-positive error rates (type I error) 2-4 times higher than in randomised phase II trials
- Increasing sample size did not correct the over-optimism of single-arm studies

Other problems with SATs

- Association of ORR with overall survival questionable at best
- Combinations still hold more promise than single drugs
- ORR limited to neoadjuvant and end-stage
- Apparently good results can make subsequent randomised trial more difficult
- May be time-inefficient except in genuinely rare tumour subsets


MRC FOCUS4
mCRC First line chemo 16 wks Stable/ responding
Diagnostic biopsy
REGISTER
Biomarker analysis during 1st 8-12 wks
A
E
B
C
D
N
ALLOCATE
BRAF mut
MSI/MMR def
PIK3CA mut
Synthetic lethality cohort
All WT
Non-strat
RANDOMISE
P
Novel agent
rebiopsy
No Rx
CAP
Primary endpoint:
PFS in the interval
Restart first line chemo on progression
rebiopsy

One FOCUS4 cohort



Single-arm Ph II *vs* Randomised Ph II

MRC Clinical Trials Unit

Single-arm Phase II for ORR:

- 27 patients (25 evaluable) recruited over 3 mos
- + 16 wks (4 mos) for full assessment of response
- + 1 mo for data checking and analysis

- Time elapsed = 7 months
- If encouraging:
  - + 6 mos to set up a randomised phase II
- Sub-total: time to start of ph II = 13 months (minimum)
- Total: 24-30 mos until ph II completed

Randomised (2:1) Phase II for PFS + ORR:

- At 9 mos: 24 pts on active arm evaluable for ORR; *plus* stage 1 PFS analysis available (81 pts randomised)
- At 16 mos: final randomised phase II PFS analysis available

Other arguments for randomised Ph II

- Randomised phase II may provide ‘No-go’ decisions almost as quickly as single arm
- ‘Go’ decisions become ‘Go-on’, with the next needed dataset already well underway
- No disadvantage if the response data are so dramatic that ready to approach regulators
- Provides a much fuller toxicity/safety profile
  - plus PD, plus data for Health Economics/HTA assessment
  - possibly plus useful translational, biomarker data, *etc.*
- The more that durable responses are critical, the better the argument for randomising & seamless ph 2/3 design

Comments / Questions?