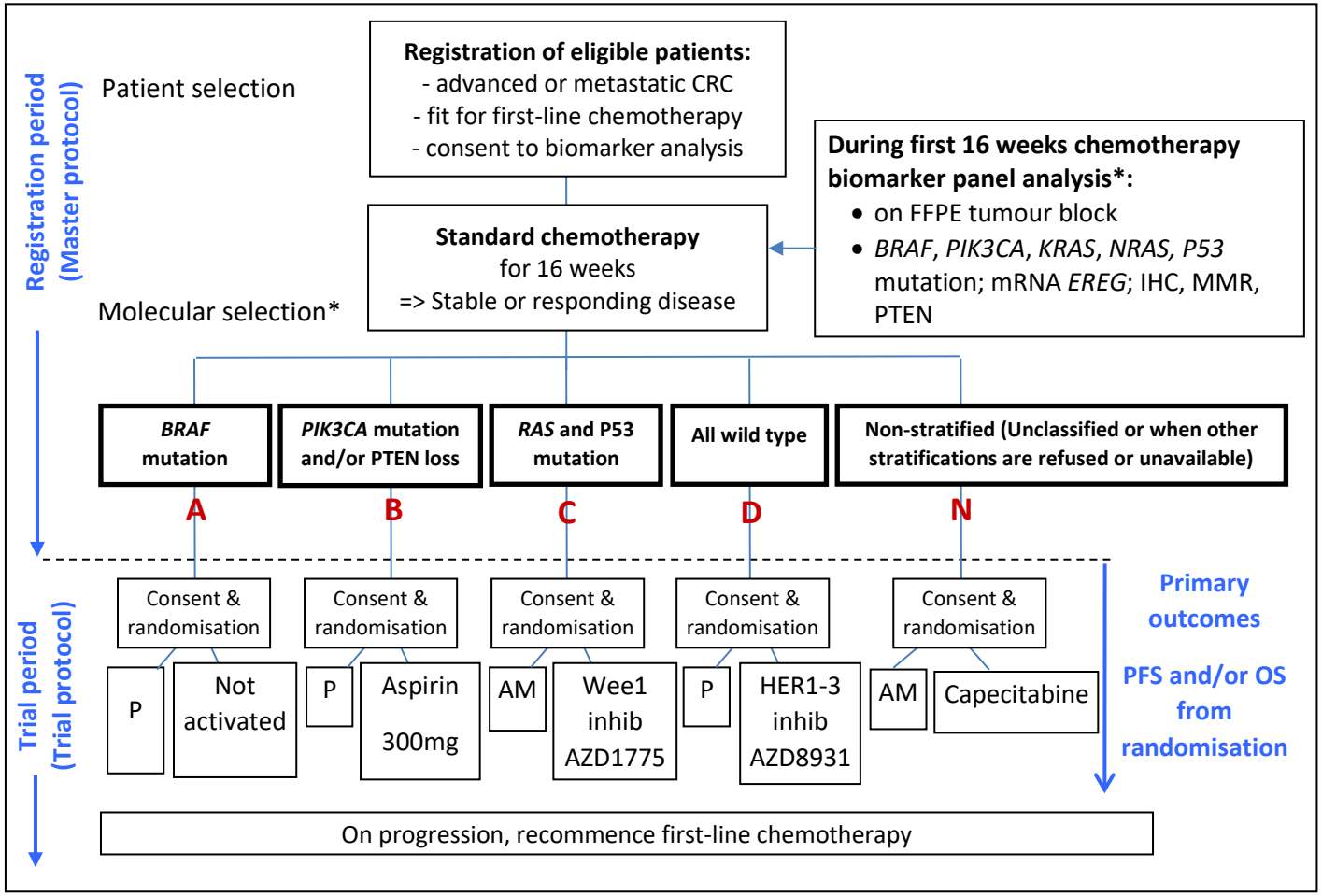
Figure 1 - FOCUS4 Trial Schema



** The molecular cohorts are arranged in a hierarchy from left to right. For example a patient with both a BRAF and a PIK3CA mutation is classified into the BRAF mutation cohort.*

P=Placebo; AM=Active Monitoring; PFS=Progression-Free-Survival; OS=Overall Survival

Figure 2 – Timelines for development and delivery of FOCUS4

Figure 3 – Key design features of FOCUS4

- Uses molecularly enriched cohorts to maximise the possibility of detecting promising new treatments
- Uses multi-stage statistical design for early detection of insufficient activity
- Tests whether activity is specific to the molecular subgroup
- Provides a trial opportunity for all patients regardless of biomarker status
- Biomarker structure can adapt to:
  - Include new
  - Drop current
  - Change existing
- Tests multiple treatments at the same time, each against its own control
- Moves seamlessly from Phase II to Phase III

Table 1 – Summary of 4 successful and 16 unsuccessful comparisons explored for addition to the FOCUS4 platform

cohort	biomarker	BM incidence	intervention	outcome
A1	BRAF V600E mutation	10%	BRAF I and MEK i	Science evolved
A2	BRAF V600E mutation	10%	Dabrafenib, trametinib + panitumumab	GSK sold oncology portfolio to Novartis. Novartis: insufficient activity to support.
B1	PIK3CA mutant or PTEN loss on IHC	22%	Dual PI3Ki/mTORi	Insufficient evidence of benefit
B2	PIK3CA mutation	12%	Aspirin	FOCUS4-B Trial
C1	KRAS/NRAS mutation	45%	MEKi + PI3Ki	Found to be too toxic in early studies
C2	RAS mutation + HLA A-2	20%	IMA 190 peptide vaccine	Company did not commit
C3A	H3K36me3 loss	<2%	Wee-1 inhibitor AZD1775	Biomarker: very low incidence of loss
C3B	RAS + TP53 double mutation	30%	Wee-1 inhibitor	FOCUS4-C Trial
C3C	ATM loss	6%	ATM inhibitor AZD 6738	Company did not support concept
D1	KRAS, NRAS and BRAF wildtype	40%	Pan-her inhib AZD8931	FOCUS4-D Trial
D2	KRAS, NRAS and BRAF wildtype	40%	MM151	Company sold asset prior to contract
D3	Triple wildtype, her2 negative	25%	Cetuximab + CDK4/6i	Pending data from SCCHN
E1	MMR deficient and POLE mutant	4%	Avelumab	Company did not support concept
E2	MMR deficient or TGFb activated	30%	Bintrafusp-alpha	EME/CRUK did not extend grant
F	Axin 2 overexpressed	9%	RXC004 porcupine inhib	EME/CRUK did not extend grant
G	Her-2 over-expressed	2%	Trastuzumab + CDK4/6i	Biomarker incidence too low
H	ALK/ROS rearrangements	2%	Crizotinib	Biomarker incidence too low
N1	Non stratified group	-	Capecitabine	FOCUS4-N trial
N2	Non stratified group	-	Add TAS-102	Global company did not support concept
N3	Non stratified group	-	Metronomic cyclophosphamide	EME/CRUK did not extend grant

Table 2 – Key learning points from stakeholder feedback

	Resource and infrastructure
1	Secure adequate funding
2	Delivering all desired outcomes for a platform trial is clearly challenging. The challenge for funders is to find a mechanism for funding and review of adaptations that facilitates delivery and minimises burden while also managing the risks involved.
3	Ideally, these trials should only be conducted in clinical trial units that have good core funding resources and a ballast of trained in-house trial and data managers who can be drawn upon temporarily at times of intense activity.
4	Activate fewer sites and stagger opening.
5	Leadership: The Chief Investigator (CI) role is paramount and must not be under-estimated with far more pressure than being a CI on a more standard trial. An engaged and enthusiastic core Trial Management Group (TMG) is vital.
6	The Clinical Trials Unit (CTU) staff must feel comfortable and encouraged to escalate any site issues to senior TMG members quickly.
7	A great training experience for CTU staff and clinical research fellows. Provide basic clinical trial training for research fellows to aid learning.
8	Site enthusiasm was inconsistent between registration and randomisation. Understand local motivations or obstacles to recruitment.
9	Trial longevity can lead to poor continuity of CTU and site staff which is disruptive in a complex trial where the design keeps adapting.
10	For trials that last many years, trial participants need better opt in/opt out arrangements on how they can be kept informed on trial progress.
	Biomarker testing process
11	Regular Quality Assurance (QA) and review of sample testing processes to identify any glitches that require modification.
12	Important to spend adequate time on biomarker work-up and optimisation as well as understanding prevalence early on before taking further.
13	Keep biomarker testing within the NHS infrastructure as much as possible with as few middle men as possible to avoid data privacy obstacles.
14	Important to have an engaged and dedicated biomarker team who can manually step in and overcome any delays to prevent patient distress.
	Trial Design
15	The Multi-Arm, Multi-Stage (MAMS) adaptive design worked well at cutting losses on poorly performing drugs early.
16	The requirement for a control arm in each comparison was important in determining any prognostic biomarker effects.
17	The need for a catch-all non-stratified trial (FOCUS4-N) proved to be successful at maximising trial opportunities for patients.
18	Important to get the protocol structure right and consult with regulatory bodies on advice for what is acceptable within the design.
19	The main issues were mainly related to pharma engagement and drug-target identification in the specific disease setting of the study. Earlier engagement in the developmental pathway for new therapies is required so that when the therapy is ready to drop into a trial, all parties have been engaged and involved with the biomarker optimisation and early drug activity assessments.
20	Funding of complementary feeder collaborations such as SCORT (which focused on understanding the biology) and ACRCelerate (which focussed on pre-clinical novel agent development) might have been beneficial if run in parallel with FOCUS4.

Table 3 – Summary of results from participating site survey

Question and response (%)	Take home message
Did inability to restart an EGFRi impact on patient selection? Agree/ strongly agree - 68% Neutral - 14% Disagree/ strongly disagree - 18%	NHS rulings on the use of eGFR inhibitors restricted recruitment and may have been a barrier to finding alternative or better therapies relevant in the RAS wild-type group.
Was having an unselected FOCUS4-N trial important? Agree/ strongly agree - 71% Neutral - 25% Disagree/ strongly disagree - 4%	An important aspect of the design that was strongly supported by sites and patients
What were the advantages and disadvantages of conducting this trial in the maintenance setting?	**Advantages:** • Fitter patients • Less acquired drug resistance • Induction chemo allowed time for biomarker testing without delaying treatment start • Less end organ impairment • Patients felt they were “trying something“ when otherwise might be having a break **Disadvantages:** • NHS England rules preventing EGFRi reintroduction • a more challenging route to registration for successful agents • additional hospital time or toxicity • Some patients progress during induction treatment and become ineligible
Did you experience any particular study challenges?	**Staff and infrastructure** • Delays with local Research & Development (R&D) department approval • Limited nursing support particularly at level 1 sites for our network • Maintaining team motivation when novel arms not open • Some challenges referring from level 1 to 2 or 3 site.

	Trial assessments • Poor capacity for RECIST reporting • Novelty of the trial biomarker panel became diluted as NHS testing rolled out.
What went well?	• Excellent CTU communications (response to queries, newsletters etc) • Novel design of an adaptive platform trial in a common solid tumour - first of its type in the UK • Easy to recruit with the window to request biomarker testing • Engaged all geographical areas within the UK with the level 1-2-3 design. • Patient information sheets were well developed.
Are platform trials the future?	• Grossly underfunded but definitely the best way to proceed compared to running endless small trials in small subgroups • Funders should have supported funding for fresh biopsies and additional translational work • Speed and efficiency of adding arms with protocol amendments • Platform allows for sub studies e.g. exercise, PET, CT DNA.