Unrivalled track record

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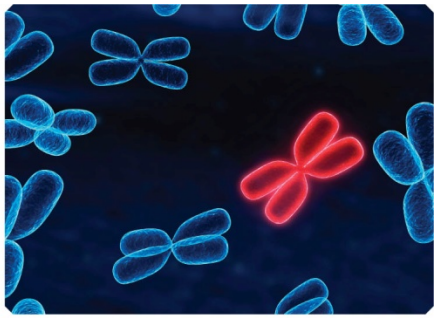

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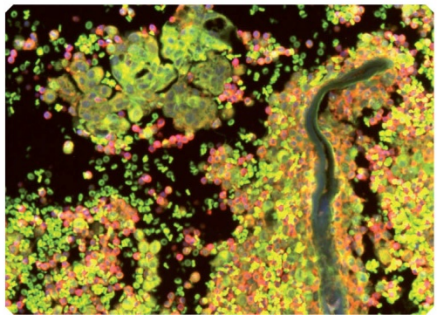

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CANCER RESEARCH UK

Practical challenges of delivering a platform trial from a trial management perspective

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NIHR Statistics Group – Early Phase Clinical Trials Meeting: 28/02/2019

Background

- Increased use of platform designs in cancer trials
- Efficiencies of platform trial designs are widely recognised (increased screening efficiency, reduced time for drug evaluation)
- Increasing awareness of operational challenges (complexity, risks, costs, regulatory and resource)[1,2,3]
- Operational challenges for CTUs and sites not always appreciated
- ICR-CTSU experience with plasmaMATCH

1. Meurer WJ, Lewis RJ, Berry DA. Adaptive Clinical Trials: A Partial Remedy for the Therapeutic Misconception? JAMA. 2012;307(22):2377–2378
2. Redman MW, Allegra CJ. The Master Protocol Concept. Semin Oncol. 2015;42(5):724-30.
3. Woodcock J, LaVange LM.Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 2017; 377:62-70

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The ROYAL MARSDEN NHS Foundation Trust

STAND UP TO CANCER standuptocancer.org.uk

CANCER RESEARCH UK

The UK plasma based Molecular profiling of Advanced breast cancer to inform Therapeutic CHoices (plasmaMATCH) Trial:

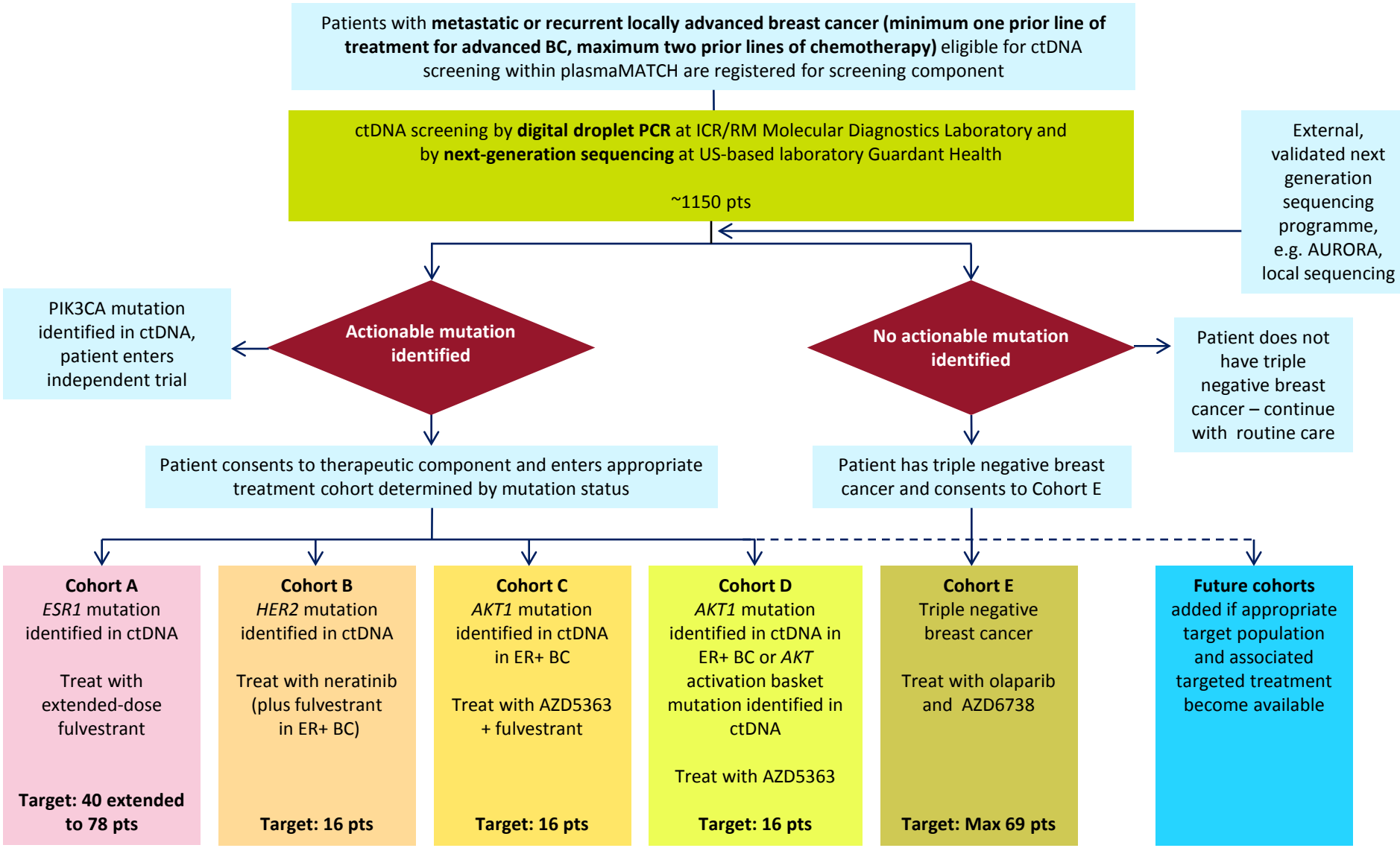
A multiple parallel cohort, open-label, multi-centre phase IIa clinical trial aiming to provide proof of principle efficacy for designated targeted therapies in patients with advanced breast cancer where the targetable mutation is identified through ctDNA screening

plasmaMATCH

Trial organisation

- Co-sponsors – The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RM)
- Coordinated by ICR Clinical Trials and Statistics Unit (ICR-CTSU)
- Chief Investigator and 5 treatment cohort leads
- Molecular screening at ICR/RM Molecular Diagnostics Laboratory
- 19 treatment sites throughout UK
- 3 funding partners – CRUK, Puma Biotechnology and AstraZeneca
- 5 IMPs
  - Fulvestrant (Cohorts A, B and C) – AstraZeneca
  - Neratinib (Cohort B) – Puma Biotechnology
  - AZD5363 (Cohorts C and D) – AstraZeneca
  - Olaparib (Cohort E) – AstraZeneca
  - AZD6738 (Cohort E) – AstraZeneca

Trial schema, patient population and biomarker stratification strategy



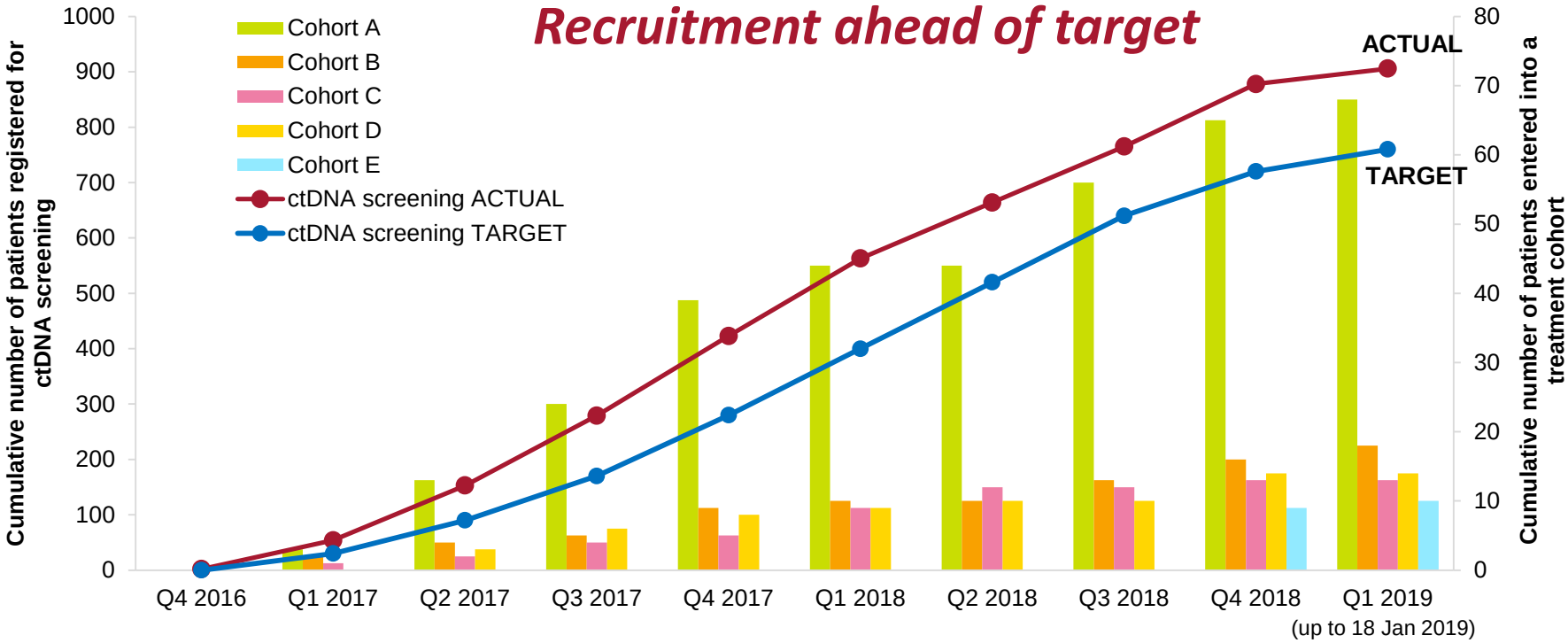
Timelines

2015

Jun-15	CRUK CTAAC grant award letter issued
Sep-15	CRUK CTAAC grant activated
Apr-16	Regulatory and ethics application submissions
Sep-16	Regulatory and ethics approvals in place
Dec-16	First site open to recruitment First patients registered
Jan-17	First patient entered into a treatment cohort
May-17	CRUK CRC amendment application for addition of Cohort E submitted
Nov-17	CRUK CRC approval for Cohort E amendment
May-18	Cohort E regulatory and ethics application submissions
Jun-18	Cohort E regulatory and ethics approvals in place
Sep-18	First site open to Cohort E
Oct-18	First patient entered into Cohort E
Q2-19	Planned closure of recruitment to Cohorts A-D
Dec-19	Planned presentation/publication of Cohorts A-D

2019

Recruitment



	ctDNA screening	Cohort A	Cohort B	Cohort C	Cohort D	Cohort E
Total up to 18 January 2019	907	68	18	13	14	10

Key Challenges – FUNDING & TIMELINES

- Understanding of trial scale and complexity – time and cost
- Appropriate funding mechanisms for platform trials
- Multiple funding partners
- Complexity of budgets and contractual arrangements
- Costings for main trial and for trial adaptations
- Increased set up times vs funders & government expectations
- Timelines for addition of new cohorts

Key Challenges – FUNDING & TIMELINES

plasmaMATCH experience

- Screening platform and trial set up funded by CRUK with individual treatment cohorts funded by pharma partners
- Complex costings for original platform and platform adaptations (planned and actual)
- Reciprocal confidentiality agreement between the cosponsors and pharmaceutical partners which allows for further companies to join at a later date
- Bespoke template agreement developed to allow easy adaption
- Same agreement with same T&Cs used for all pharma partners
- Pharma partners required to provide drug distribution
- Added complication of combination arms
- Trial opened to recruitment 15 months from grant activation
- Lengthy approval process for addition of new cohort (16 months including 6 months for CRUK to approve amendment)

Key Challenges – REGULATORY

- Lack of regulatory framework for platform trials
- HMA CTFG recommendation paper on the Initiation and Conduct of Complex Clinical Trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf
- Addition of new cohorts vs EoT
- MHRA regulatory advice meetings

Key Challenges – REGULATORY

plasmaMATCH experience

- Didn't have a regulatory advice meeting at the outset
- Delay in obtaining MHRA approval due to Grounds for Non Acceptance surrounding use of non-CE marked ctDNA screening assays and use of ctDNA screening in comparison to gold standard which MHRA defined as a test performed on tumour tissue
- TC with the MHRA medical assessor and subsequent communications (ie when adding new cohorts) helped improve understanding on both sides
- Regulatory submission to approval 5 months

Key Challenges – PROTOCOL

- Modular vs single protocol
- Future proofing for additional cohorts – plans for future adaptations
- Managing frequent and often complex protocol amendments

Key Challenges – PROTOCOL

plasmaMATCH experience

- Single protocol covering the screening platform plus individual treatment cohorts
- One document for sites to reference
- Screening and common elements described in the main body of the protocol with cohort specific appendices
- Adding in a new cohort had limited impact on main body of the protocol
- Consistent visit schedules across cohorts helped with CRF and database development

Key Challenges – TRIAL MANAGEMENT

- TM workload
- Implementing a complex protocol across trials sites – training and on-going support
- Volume of documentation – multiple PIS&ICFs
- Managing multiple, often complex amendments
- Managing multiple drug ordering across multiple sites
- Management of reference safety information - multiple IMPs/frequent IB updates
- Implementing new treatment cohorts in on-going trial
- Risk management
- Fast moving scientific field
- Technically challenging

Key Challenges – TRIAL MANAGEMENT

plasmaMATCH experience

- Conflicting and increased demands on TM resource (6 trials in 1)
- More high level project management input required
- More on-going support and training for sites
- Frequent amendments (update to eligibility criteria, addition of second screening method, extension of Cohort A, addition of Cohort E, PIS updates due to GDPR and IB updates) – ramifications across multiple documents and IT systems
- Re-costings for planned cohort extensions/new treatment cohorts
- Faster than anticipated recruitment rates – challenging to implement new treatment cohorts and close existing cohorts within the scope of the screening platform

Key Challenges – TECHNICAL COMPLEXITY

plasmaMATCH experience

- Close collaboration with central laboratory
  - Robust sample management procedures
  - Timely analysis
  - Timely feedback of results
- Sites require more ongoing support and training
- Feedback of ctDNA screening results to sites
  - Cover sheets to aid interpretation at sites
- Introduction of second screening method (via Guardant Health) to platform
  - Complexity of Guardant360 results reports (Panel of 72 genes sequenced only 3 actionable within plasmaMATCH)
  - TMG review required to confirm actionable mutations
  - Cover sheet to aid interpretation at sites

Key Challenges – DATA MANAGEMENT

- Single database vs separate databases for screening component and individual treatment cohorts
  - Database size/complexity vs performance
  - Ease of use at sites
  - Building and testing time
- Automation of processes vs time to set up trial
- DM workload and conflicting demands
- Complexity of DM activities (sample and data collection)
  - Clinical and randomisation database build and testing
  - Database change requests
  - Data cleaning
  - Safety monitoring
  - Sample management

Key Challenges – DATA MANAGEMENT

plasmaMATCH experience

- Single database for screening component and cohorts A-D so only 1 database for sites to access
- Consistency of visit schedules across cohorts simplified database development and testing
- Staged release of database to meet trial set up timeline expectations
- Separate database for cohort E due to increasing database size and performance issues
- Checks built into randomisation system to ensure correct mutation for treatment cohort entry
- Lack of time to set up new systems to allow more automation of process
- Implementing amendments – ramifications across multiple systems
- Conflicting and increased demands on DM resource (6 trials in 1)
- Faster than anticipated recruitment rates – difficulty keeping on top of accumulating data

Key Challenges – IMPACT ON SITES

- Protocol complexity
- Technical complexity
- Novel compounds and combinations
- Administrative burden associated with multiple cohorts
- Data volume

Key Challenges – IMPACT ON SITES

plasmaMATCH experience

- Administrative burden of volume of documentation (separate PIS&ICFs, GP letters etc. for each cohort)
- Burden of data collection for all screened patients
  - As required to ensure NIHR portfolio accrual recognition for all patients screened

eCRF completion at Royal Marsden Hospital up to 18 January 2019

Site	Number of registered patients	Number of treatment cohort patients	Number of eCRFs expected	Number of eCRFs received	Percentage eCRFs received
Royal Marsden Hospital, London	198	36	3842	3065	79.8%

- Burden for screening only sites not off-set by income
- Successful recruitment driven by a small number of highly experienced treatment sites

Key lessons learnt

- Resource intensive – don't underestimate workload
- Multiple funding sources required
- Importance of regulatory advice meeting
- Template agreements to ensure consistency of negotiations
- Pharma partners to provide drug distribution
- Integration of the screening and treatment components in same protocol
- Consistent assessment schedules for treatment cohorts
- Separate databases for screening component and each treatment cohort
- Reduce level of data collected for screening only patients
- Challenging for sites - successful recruitment driven by a small number of highly experienced treatment sites

Key benefits and successes

- One regulatory and ethics approval
- Close partnership between CI, central laboratory and CTU
- Individual clinical lead for each cohort – empowers community and shares responsibility and workload
- Attractive to participating sites – molecular screening and multiple treatment options for patients
- Recruitment ahead of target
- Reporting of 4 cohorts within 3 years of FPFV

Conclusions

- Platforms are challenging logistically and technically for CTUs and participating sites
- Challenges can be overcome with sufficient resources and planning
- Complexity and workload should not be underestimated

Acknowledgements

- plasmaMATCH Trial Management Group
- Laura Moretti, Sarah Kernaghan, Katie Wilkinson & Sue Martin at ICR-CTSU
- MRC CTU – Stampede and FOCUS4
- Cancer Research UK Clinical Trials Unit (CRCTU) – Lung Matrix

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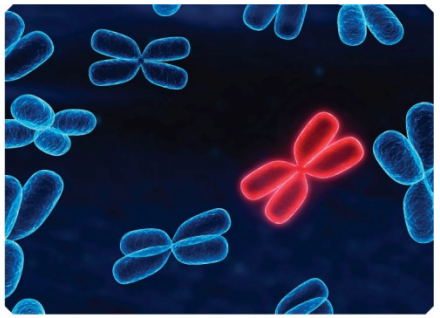

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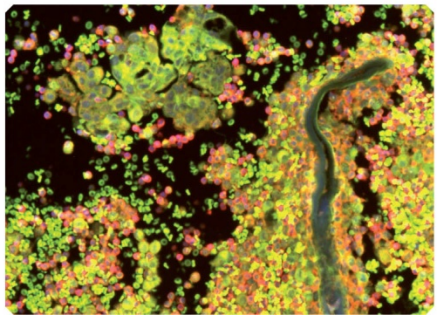

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