ICR The Institute of Cancer Research

CANCER RESEARCH UK

in partnership with The ROYAL MARSDEN NHS Foundation Trust

A multiple parallel cohort, open-label, multi-centre phase IIa clinical trial of circulating tumour DNA screening to direct targeted therapies in patients with advanced breast cancer (CRUK/15/010)

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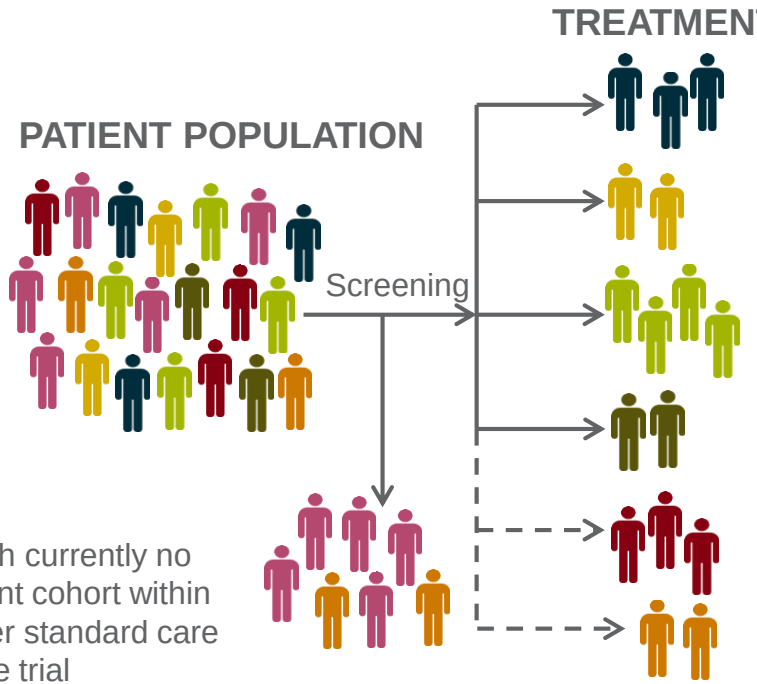
Introduction

- Circulating tumour DNA (ctDNA) is found in the plasma of over 90% of patients with advanced breast cancer (BC)
- Screening for the presence of mutations in ctDNA provides a current assessment of the genetic profile of the patient's recurrent BC
- The plasmaMATCH trial is designed to assess the potential of ctDNA screening to direct targeted therapies in patients with advanced breast cancer
- plasmaMATCH aims to determine the efficiency of the dynamic umbrella trial platform design in providing proof of principle efficacy for designated targeted therapies

plasmaMATCH umbrella trial platform design

- Umbrella trial platform consisting of a ctDNA screening component and a therapeutic component

Biologically different sub-groups of patients with advanced BC identified and triaged into distinct treatment groups (cohorts) to receive targeted therapy hypothesised to be of benefit to specific sub-group



Standalone cohorts with specific eligibility criteria and safety monitoring tailored to each treatment

Individual treatment cohorts will not be compared with other treatment cohorts

Sub-groups with currently no relevant treatment cohort within trial treated as per standard care outside trial

Dynamic trial design – potential future cohorts added as new targeted treatments become available for further sub-groups

plasmaMATCH trial design

Patients with metastatic or recurrent locally advanced breast cancer eligible for ctDNA screening within plasmaMATCH are registered for screening component

Blood sample sent to central laboratory for analysis by digital PCR using ctDNA assays for hotspot mutations in *ESR1*, *HER2*, *AKT1* and *PIK3CA*, with *HER2* copy number assessment

Actionable mutation identified in ctDNA screening

PIK3CA mutation status also reported to facilitate entry into trials outside of the context of plasmaMATCH

Eligible patients enter therapeutic component for treatment with targeted agent until disease progression

Cohort A	**Cohort B**	**Cohort C**	**Cohort D**	**Future Cohorts**
ESR1 mutation Treat with extended-dose fulvestrant	*HER2* mutation Treat with neratinib (plus fulvestrant in ER+ BC)	*AKT1* mutation in ER+ BC Treat with AZD5363 + fulvestrant	*AKT* activation basket mutation identified in ctDNA or in tumour tissue sequencing outside of plasmaMATCH Treat with AZD5363	May be added by substantial amendment in the case of new diagnostic/ therapeutic targets as the trial progresses

Number of centres ~50 UK Screening Sites, of which ~25 sites will also be Treatment Sites

Recruitment target

- ctDNA screening component: ~1000 patients with metastatic or recurrent locally advanced BC who have received prior systemic treatment in the advanced setting
- Therapeutic component: Cohort A – 40 patients; Cohorts B–D – 16 patients in each

Objectives and outputs

- Primary objective: to assess the safety and activity profile of targeted therapies in patients with targetable mutations identified by ctDNA screening

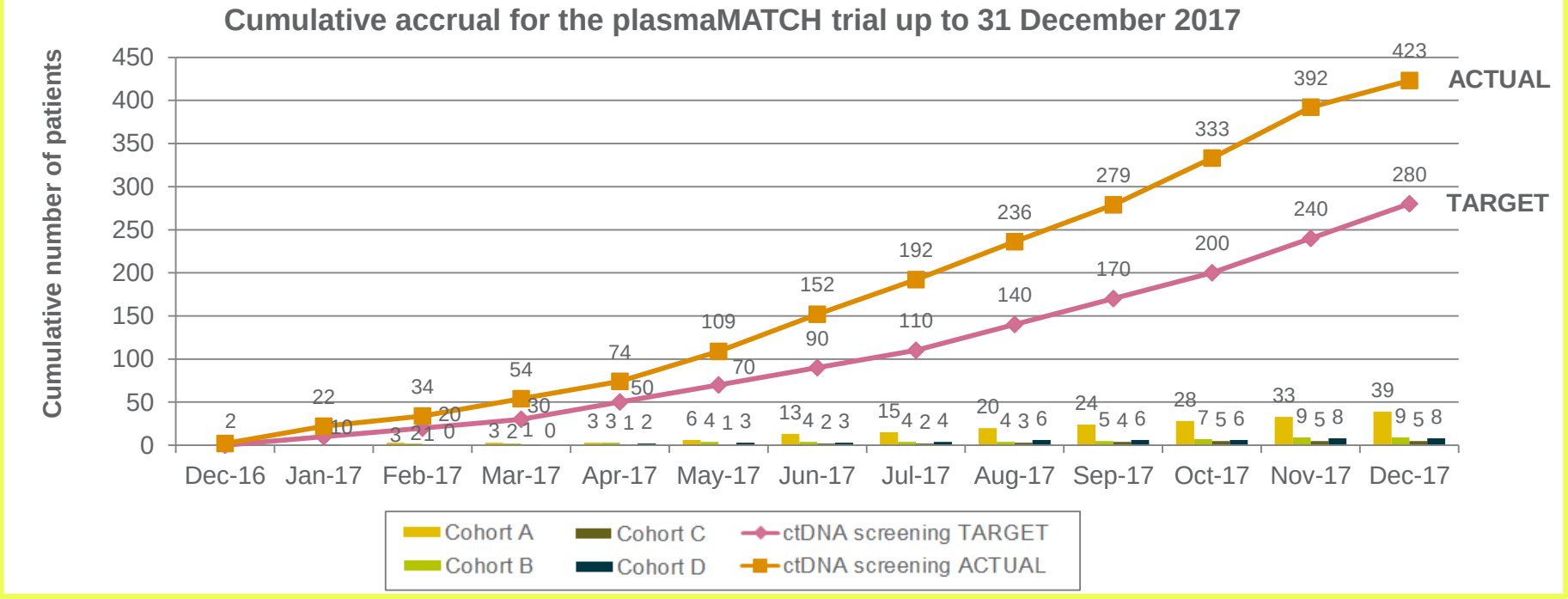
- Secondary objectives:
  - Determination of frequency of targetable genetic mutations in a large advanced breast cancer patient population
  - Proportion of patients with targetable mutations who enter a therapeutic cohort

- plasmaMATCH will assess whether ctDNA is a feasible multi-centre screening tool for detecting aberrations in advanced breast cancer

- Planned translational analyses will:
  - Assess level of agreement between ctDNA mutation status & tissue mutation status for patients entering a treatment cohort
  - Aim to determine whether serial ctDNA assessment on treatment can be used to monitor response & development of resistance to targeted therapies

Current status

- Opened to recruitment on 15 December 2016
- 14 Screening and Treatment Sites open to recruitment to date



Site status

- Accrual by Screening and Treatment Site up to 31 December 2017

Centre Name	Date open to recruitment	Registration for ctDNA screening	Cohort A	Cohort B	Cohort C	Cohort D
Royal Marsden Hospital, London	15/12/2016	104	9	4	1	6
The Christie Hospital, Manchester	11/05/2017	91	2	2	2	0
Royal Marsden Hospital, Sutton	15/12/2016	53	5	0	1	2
West of Scotland Beatson Cancer Centre	03/05/2017	39	3	0	0	0
Royal Devon and Exeter	05/05/2017	36	5	0	0	0
Addenbrooke's Hospital	11/04/2017	31	8	2	1	0
University College London Hospital	01/03/2017	23	2	0	0	0
Oxford University Hospitals NHS Trust	21/08/2017	19	4	1	0	0
Western General Hospital, Edinburgh	22/06/2017	12	0	0	0	0
University Hospitals Bristol NHS Foundation Trust	24/11/2017	4	0	0	0	0
Barts Health NHS Trust	30/06/2017	3	1	0	0	0
Velindre Cancer Centre	24/10/2017	3	0	0	0	0
Weston Park Hospital, Sheffield	23/11/2017	3	0	0	0	0
Royal Bournemouth Hospital	23/02/2017	1	0	0	0	0
Royal Cornwall Hospital	14/11/2017	1	0	0	0	0

- Additional Screening and Treatment Sites in set up
  - Belfast Health and Social Care Trust
  - Clatterbridge Cancer Centre, Liverpool
  - Derriford Hospital, Plymouth
  - Guy's and St Thomas's Hospital, London
  - Kent Oncology Centre, Maidstone
  - Nottingham University Hospitals NHS Trust
  - Queen Elizabeth Hospital, Birmingham
  - Southampton Oncology Centre
- Set up of Screening Only Sites to begin Q1 2018

Mutation prevalence in first 342 patients

- As of 23 November 2017, 342 patients had ctDNA screening results available
- We report the results of prospective ctDNA mutation testing in these patients
- Mutation prevalence is presented with corresponding exact 95% confidence intervals (CIs) both overall and excluding 16 patients who were known to have mutations from a prior screening program
- Patients with more than one mutation are included once in each relevant row

Mutation	Prevalence (95% CI)	Prevalence excluding 16 patients with known mutations (95% CI)
ESR1	94/336: 28% (23%–33%)	85/320: 27% (22%–32%)
HER2	13/333: 4% (2%–7%)	9/317: 3% (1%–5%)
AKT1	14/335: 4% (2%–7%)	11/319: 3% (2%–6%)
PIK3CA*	85/336: 25% (21%–30%)	81/320: 25% (21%–30%)
*No corresponding plasmaMATCH treatment cohort		

Mutation prevalence in first 342 patients (cont.)

- Of the 165 patients with at least one mutation detected
  - 125 patients had a single mutation detected and
  - 40 of whom had more than one mutation detected (27 ESR1+PIK3CA, 5 ESR1+AKT1, 3 ESR1+HER2, 3 HER2+PIK3CA, 1 AKT1+PIK3CA and 1 ESR1+HER2+AKT1)

- ctDNA results were reported in a median of 8 (IQR: 7, 10) working days

- 111 patients had at least one ***actionable*** mutation detected that would facilitate entry into plasmaMATCH
  - 47 of whom have entered a cohort & 38 of whom will not enter a cohort

- An additional 4 patients have entered Cohort D on the basis of a mutation detected in an alternative tumour sequencing initiative

Mutation prevalence in first 342 patients by phenotype

Phenotype[1]	ER/PgR +ve, HER2 -ve		ER/PgR +ve, HER2 +ve		ER/PgR -ve, HER2 +ve		ER/PgR -ve, HER2 -ve		Unobtainable /Missing		Total	
	N=182		N=28		N=17		N=39		N=70		N=336	
	N	%	N	%	N	%	N	%	N	%	N	%
***ESR1* mutation**	64	**35**	10	**36**	0	**0**	0	**0**	20	**29**	94	**28**
***HER2* mutation**	5	**3[3]**	2	**7**	1	**6[4]**	2	**5**	3	**4**	13	**4[5]**
***AKT1* mutation**	8	**4[6]**	0	**0**	0	**0**	3	**8**	3	**4**	14	**4[7]**
***PIK3CA* mutation**	51	**28**	9	**32**	2	**12**	3	**8**	20	**29**	85	**25**
No mutation[2]	79	**44[3]**	12	**43**	13	**81[4]**	32	**82**	34	**49**	170	**51[5]**

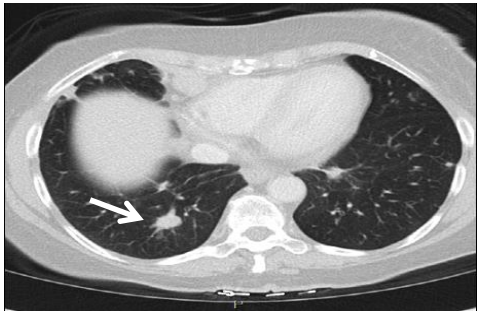
[1]ER/PgR/HER2 status taken from most recent progression if available, otherwise from initial diagnosis
[2]Patients were included if *ESR1*, *HER2*, *AKT1* and *PIK3CA* mutation results were all negative
[3,4,5]Denominators are 180, 16 and 333 respectively due to failed/inconclusive/pending results
[6,7]Denominators are 181 and 335 respectively due to a failed result

Treatment guided by ctDNA analysis

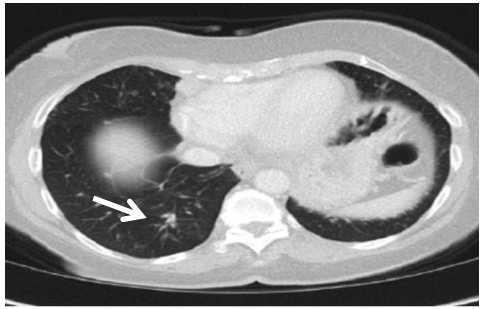
AZD5363 + fulvestrant

***AKT1* mutation**

Baseline



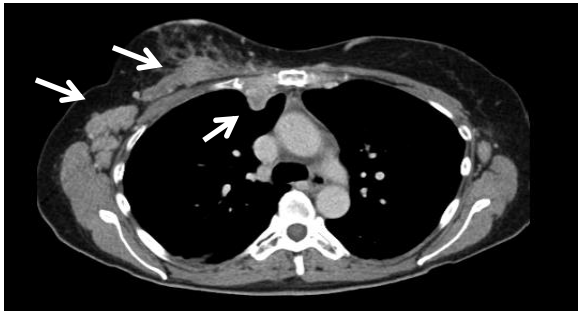
8 months (ongoing)



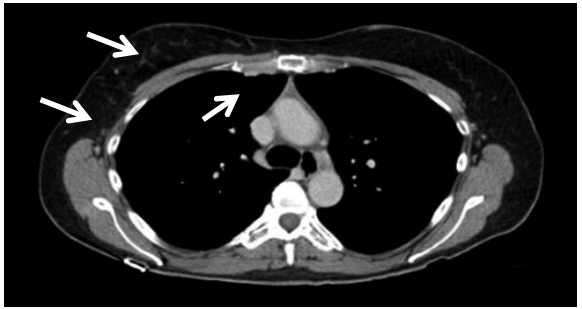
Neratinib + fulvestrant

***HER2* mutation**

Baseline



6 months (ongoing)



Conclusions

- plasmaMATCH ctDNA screening demonstrates the feasibility of recruiting patients with advanced BC into a screening platform for ctDNA assessment of mutation status, with a high rate of subsequent recruitment into matching therapeutic cohorts

- ctDNA screening within plasmaMATCH confirms the high rate of *ESR1* mutations in advanced ER positive BC, with also a higher than anticipated rate of *AKT1* and *HER2* mutations

- *HER2* mutations were also detected at a low frequency in patients with *HER2* amplified cancer, all of whom had received HER2 directed therapy

- Using ctDNA as a screening tool for rare variants in patients with advanced BC in routine clinical practice may lead to a reduction in the number of patients undergoing invasive biopsies and potentially result in substantial cost savings for the NHS

Plans for 2018

- Protocol amendment approved (in process of being implemented at sites)
  - To enable blood samples to be sent to an external laboratory based outside of the EU (Guardant Health) for ctDNA next-generation sequencing
- Protocol amendment in development
  - Addition of Cohort E, which will recruit patients with triple negative breast cancer (TNBC) who do not have an actionable mutation identified at ctDNA screening for entry into Cohorts A-D
- Set up of Screening Only Sites to begin early 2018

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