Platform Trials – The Academic Perspective

RARE TUMOURS – IDEAL FOR THE ACADEMIC PLATFORM TRIAL

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Rare Cancers

- Cancer defined as rare if less than 6 in 100000 people are diagnosed per year
- 24% of cancers diagnosed each year are rare cancers
- Academic platform trials are the ideal trial for finding new drugs for rare cancers
- Globally there are a number of national trials asking the question “Can we treat with genotype matched medicines, agnostic to tumour histological type” – trials include rare cancers and common cancers with rare actionable mutations
- Goal – to find potential new therapies for rare cancers and enable faster development of therapies for these cancers in the future

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To discuss today

- The Determine Trial – The UK rare cancer platform trial
- Collaborations – PRIME-ROSE and beyond
- How are we ensuring that we maximise the likelihood of finding new treatments for rare cancers
- How we are responding to the rapidly changing treatment landscape
- Bespoke route of approval by the payers – mechanisms of payer/reimbursement are all specific to each country (The CDF and NICE in England)

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The DETERMINE Trial

(Determining Extended Therapeutic indications for Existing drugs in Rare Molecularly-defined Indications using a National Evaluation platform trial)

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Bionow Healthcare Project of the Year Award WINNER

bionow Awards 2022

Aims of DETERMINE

DETERMINE is an umbrella, basket platform trial evaluating genotype-matched targeted agents outside of their licensed indication in **rare* adult, TYA and paediatric cancers** with actionable genomic alterations

Aims

1. Translate positive findings to the NHS (**Cancer Drugs Fund**) to provide new treatment options for patients with rare malignancies

2. Build a rich translational package to better understand the molecular (genomic, transcriptomic and immune) context behind response to targeted therapies

* Defined as <6 in 100,000/year (RARECARENet. RARECARE - Surveillance of Rare Cancers in Europe, International rare cancers initiative. Lancet Oncol 2013; 14: 109–110)

CANCER RESEARCH UK

The largest charitable funder of cancer research in the world

It funds around 50% of publicly funded cancer research in the UK

The majority of our funding comes through public donations.

The money raised is spent on research, information and influencing.

Funds high-impact research across the research pipeline through a variety of mechanisms

In 2022/23, the total research spend was

- £415m

Together we are beating cancer

Centre for Drug Development (CDD)

Based at CRUK's headquarters, we are a multidisciplinary team of over 100 scientists, physicians and operational specialists with expertise across regulatory driven drug development

Translational & Medical Sciences

Quality, Regulatory, PV & Medical Writing

Study, Project & Portfolio Management

CENTRE FOR DRUG DEVELOPMENT

Clinical Operations & Data Management

Drug Supply & Manufacturing

Business Development & Legal

DETERMINE

CDD experience & track record

Extensive clinical development experience and proven track record of delivering early phase trials

170

early-phase trials delivered with novel cancer drugs

14

agents under active development in our current portfolio

6

agents registered as medicines

including:

Zytiga® (abiraterone acetate)

Rubraca® (rucaparib) tablets

Temodal® temozolomide

MORE THAN 60

agents taken in to first-in-human clinical trials

14

first-in-class agents clinically investigated

100%

success rate with regulatory applications to the Medicines & Healthcare products Regulatory Agency

29

collaborations under the Clinical Development Partnerships (CDP) initiative

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DETERMINE – a collaborative effort

The DETERMINE team is comprised of multiple experienced clinicians and researchers that will be working closely with CRUK and its various partner organisations

Key individuals

Dr Krebs
CI/Clinical lead
MANCHESTER 1824
The University of Manchester

Dr Marshall
Paediatric lead
The ROYAL MARSDEN
NHS Foundation Trust

Prof Middleton
Translational lead
UNIVERSITY OF BIRMINGHAM

Prof Billingham
Stats lead
UNIVERSITY OF BIRMINGHAM

Dr Chaturvedi
Pathologist lead
The Christie NHS
NHS Foundation Trust

Miss Gath & Mr Burchill
Patient representatives
voice science for patient advocates
Vision On Information, Confidence & Engagement

Key organisations

Sponsor and Commercial
CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT

Trial delivery
ecmc

Co-Investigators / Collaborators
- Clinical trial experience
- Translational research (ctDNA, genomics)

Pharma partners
Roche
NOVARTIS

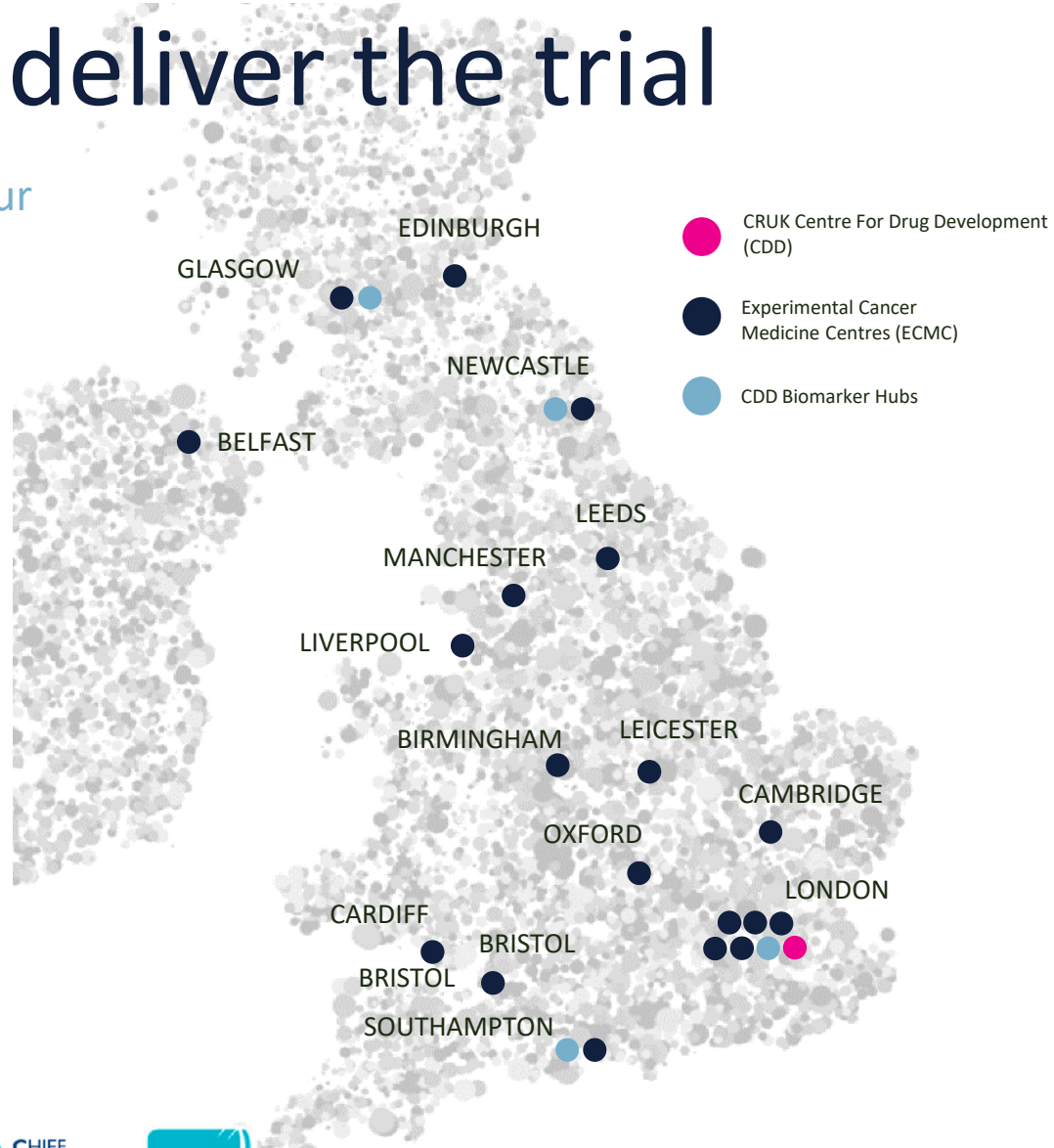
CDF
NHS England

DETERMINE

Team Science essential to deliver the trial

CRUK's infrastructure investments act as a pivotal enabler for our clinical research and development activities.

- Leverage expertise of CRUK's network of scientific and clinical investigators to design, sponsor and deliver science-driven early phase trials.
- Unique network of Experimental Cancer Medicine Centres (ECMCs) integrating NHS centres and research institutions.
- World-class translational, clinical and operational expertise.
- Multi-centre trials delivered across network of 20 clinical centres, with access to a broad UK adult and paediatric patient population.
- CDD Biomarker hubs to support translational science.

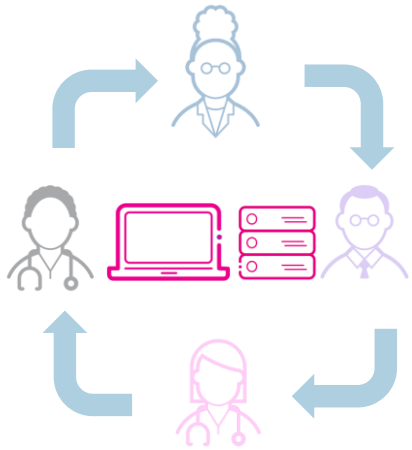


ecmc Jointly funded by: CANCER RESEARCH UK NIHR | National Institute for Health Research Ymchwil Iechyd a Gofal Cymru Health and Care Research Wales CHIEF SCIENTIST OFFICE HSC DETERMINE

Data pooling with equivalent trials in the EU through the PRIME-ROSE* consortium

DETERMINE data will be shared and aggregated with data from similar platform trials across Europe as part of its role as an **Associate Partner of the Horizons Europe-funded 'PRIME-ROSE' consortium**

24 partners collaborating across 18 countries…



PRIME-ROSE

Funded by the European Union
Grant no. 101104269

A key objective of the consortium is to **develop a shared data platform to:**

- ✓ Enable data sharing between trials
- ✓ Aggregate data for overlapping cohorts to support review by regulatory agencies

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* PRecisIon Cancer MEdicine RepurpOsing SystEm Using Pragmatic Clinical Trials. Press release

Trial Design

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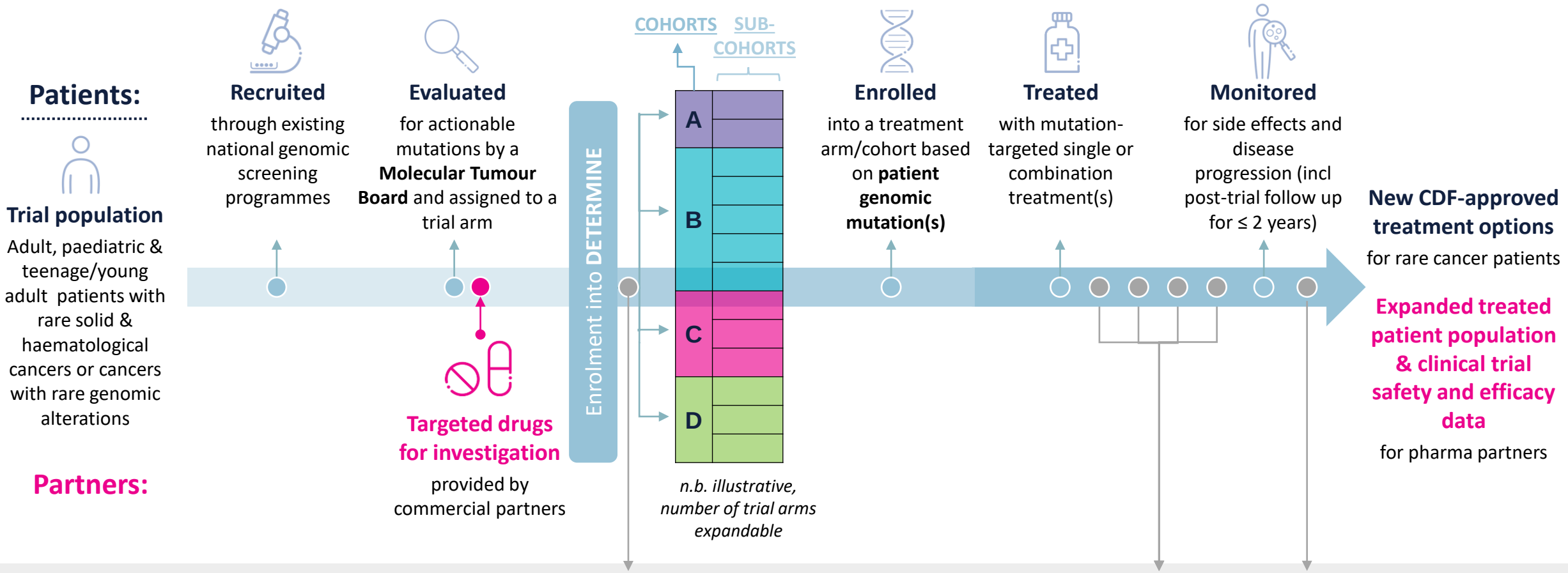
Trial overview



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Patient recruitment

Given the costly nature and high attrition rates of pre-screening programmes, DETERMINE is recruiting patients through **existing national screening programmes**

NHS Genomic Medicine Service	TARGET National study	SMPaeds study	Other screening programs
• 7 genomic hub labs • Aiming to offer sequencing as part of standard of care for all cancer patients	• 18 adult-recruiting centres • ~6k advanced solid cancer patients to be recruited across 5 years	• 20 paediatric-recruiting centres • Routine analysis of biopsies from all children with solid tumours who relapse in the UK	• Existing screening programmes e.g., IMAGINE in Scotland • Also includes commercial trials that have screening programmes embedded

- ✓ **Use of multiple national screening programmes that incorporate screening as part of routine / standard care**
- ✓ **Proven recruitment success from other umbrella trials using similar approaches** e.g. over 5 years, the TAPUR trial (U.S.) recruited 3581 patients and the DRUP trial (Netherlands) recruited 950 participants - both without use of a pre-screening programme

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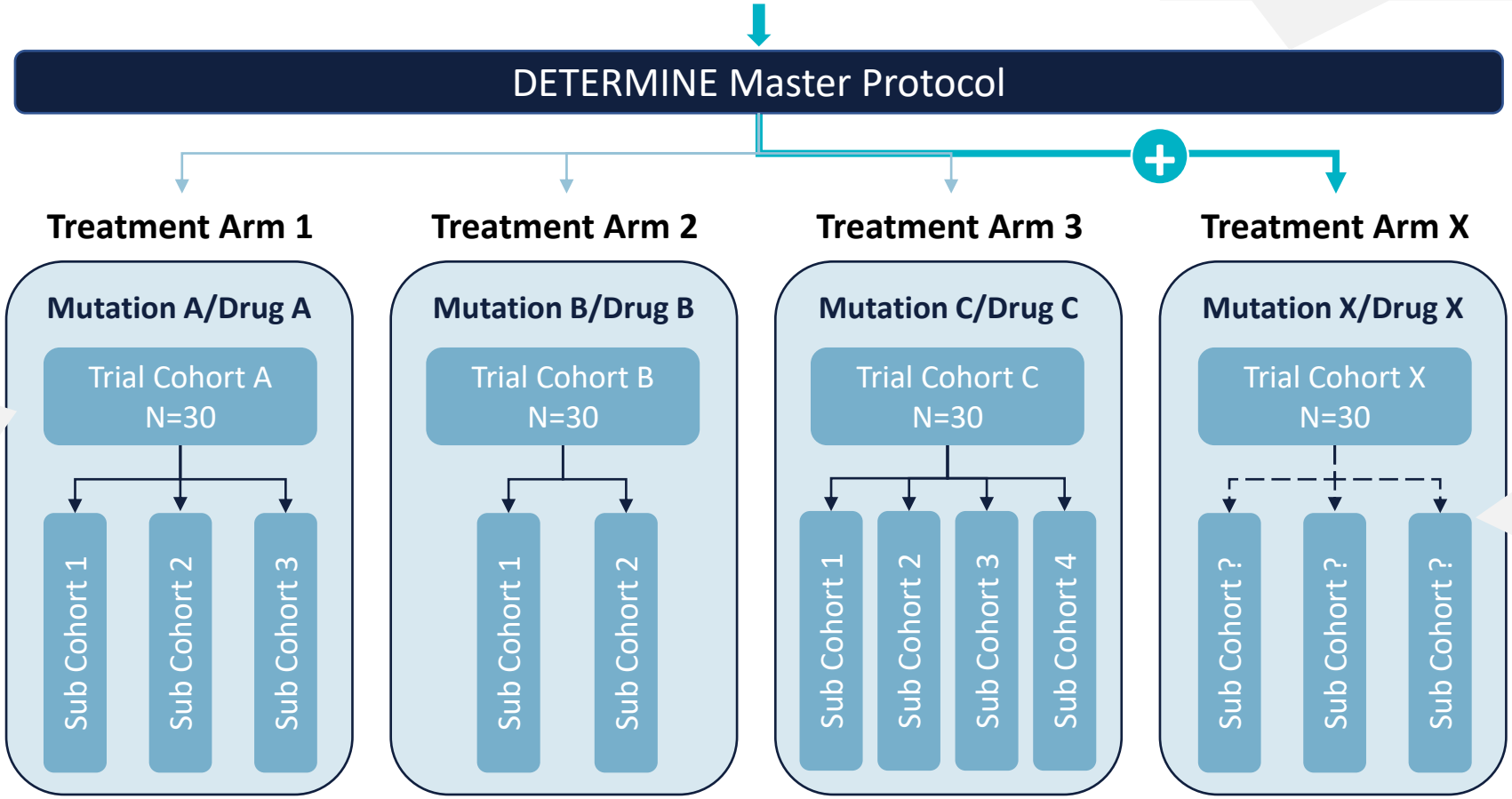
Umbrella-basket design

'Umbrella' – master protocol allowing new agents to enter and existing agents to leave the trial in a defined, approved process

Additional treatment(s) provided by new or existing commercial partners



'Basket' – each trial cohort is a basket of different tumour types, genomic complexity etc.

Sub-cohorts may branch off from the initial trial cohort to maximise success

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Existing treatment arms

Partner	Drug	Mechanism of action	Treatment arm (TA) / Trial cohort
Roche	Alectinib (Alcensa)	ALK inhibitor (TKI)	ALK positive
	Atezolizumab (Tecentriq)	PD-L1 inhibitor	high tumour mutational burden TMB> 10 microsatellite instability-high (MSI-high) or proven constitutional mismatch repair deficiency (CMMRD) disposition
	Entrectinib (Rozlytrek)	ROS1	ROS1 gene fusion positive
	Trastuzumab / Pertuzumab combo	HER2 inhibitor	HER2 amplification HER2 activating mutations
	Vemurafenib / Cobimetinib combo	MEK/BRAF inhibitors (TKI)	BRAF V600 mutations

New treatment arm

Expected to open Q2-24

Partner	Drug	Mechanism of action	Treatment arm (TA) / Trial cohort
NOVARTIS	Capmatinib (Tabrecta)	MET	MET amplification.

Translational studies

Patient sample collection enables translational studies to gain greater insights into cancer biology, and provides potential to discover new therapeutic targets and identify factors affecting differential treatment response.

Whole genome sequencing	Explore tumour genomic complexity, mutational signatures, clock-like mutational processes and provide a detailed molecular portrait of rare cancers.
Total RNA sequencing	Evaluate gene expression patterns, alternative splicing, gene fusion detection and functional relevance of copy number gain.
Immune landscape	Assess immune microenvironment and spatial immune heterogeneity, with potential for predictive biomarker identification
Epigenomics	Evaluate epigenetic changes in tissue and blood that may contribute to the development and progression of cancer.
ctDNA analysis	Enable monitoring of disease evolution and novel resistance mechanisms to targeted agents

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Overview of endpoints, ongoing DRUP-like trials, incl DETERMINE

Ongoing DRUP-like clinical trials – overview of endpoints	Trials							
Study Endpoints	**DRUP**	**IMPRESS**	**FINPROVE**	**Pro-Target**	**MEGALIT**	**Most Plus**	**POP*** **	**DETERMINE**
Primary endpoints								
% of patients that are treated based on their molecular tumor profile	X	X		X*	X	X	X*	
Objective tumor response	X	X		X	X	X	X*	X
Disease control (objective complete or partial response or stable disease) at 16 weeks after treatment initiation)	X	X	X	X	X	X	X	X**
Treatment-related grade ≥3 and serious adverse events	X	X	X*	X	X*		X*	X*
Secondary endpoints								
Progression-free and overall survival	X	X	X	X	X	X	X	X
Duration of treatment on study (time on drug)	X	X	X	X	X	X	X	X
Best overall response			X		X	X	X	X
Estimate percentage of patients eligible for analyses only by liquid biopsies because:		X					X	
i) Biopsy is not possible or ii) Primary biopsy is exhausted and re-biopsy is not possible								
Explore resistance mechanisms		X			X	X		
Time to initiate therapy		X					X	
Actionable target concordance between genomic analysis results from the Foundation Medicine platform F1CDx with that from similar local analysis					X			
Growth Modulation Index defined as time to progression with trial treatment to time to progression on most recent prior line of therapy								X
% of patients submitted to tissue biopsy across tumor types							X	
Exploratory endpoints								
Description of concordance between mutational profile of pre-treatment tumor biopsies and mutational profile according to tumor profiling tests that were used to enroll patients	X*	X		X	X	X	X	
Tumor response according to iRECIST in patients treated with checkpoint inhibitors	X	X					X	
Tumor response according to PET response criteria in solid tumors (PERCIST) in patients with solid tumors and iPERCIST in patient treated with immunotherapy							X	
Compare ctDNA and tumour DNA analyses - results and timelines		X			X	X	X	
Turn-around-time from biopsy (tissue and/or liquid) requisition to molecular testing results		X						
Cost consequence analysis of tissue versus liquid		X						
Changes in patient reported outcome measurements (PROMS) and Health-Related Quality of life (EQ-5D, QLQ-30)		X				X*	X*	X*
Evaluate the effect of different reimbursement schemes		X						
Evaluate resource use, costs and health outcomes by means of both disease specific and generic quality of life instruments		X						
Decision rule for evaluating cost-effectiveness		X						X*
Objective complete or partial response or stable disease at 16 weeks after discussion in molecular tumour board for patients NOT allocated to IMPRESS-cohort		X						
Artificial intelligence in RECIST evaluation		X						
Determine frequency of findings indicating germline alteration		X					X	
Compare ESCAT with Meric-Bernstam-guidelines		X					X	
% of patients with an actionable variant detected leading to treatment with a targeted molecular therapy			X		X			
Compare the efficacy and safety outcomes in patients according to the presence of concomitant germline and somatic mutations							X	
Microbiome composition and functional/metabolic profile assessment and changes from baseline							X	

100% similarity across trials
87.5% similarity across trial
75% similarity across trial
62.5% similarity across trial (5 of 8)
50% similarity across trial
37.5% similarity across trial (3 of 8)
25% similarity across trial (2 of 8)

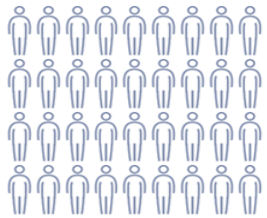
*listed as secondary endpoint in protocol
***draft protocoll from August 2022
Right: Colour coding used in the table

PRIME-ROSE
Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials

Bespoke route to approval

DETERMINE will generate an alternative, more efficient route to indication expansion for rare cancers, enabling pharma partners to avoid the high costs of traditional, single-arm trials

TRADITIONAL PATHWAY



Large 'N' required due to trial design and diverse patient cohorts

Phase Ib/II or Phase II single-arm RCT — **N = ~25-100**

Phase III single-arm RCT — **N = ~100s-1,000s**

NICE submission

- **Approval** — Safety and efficacy data satisfies NICE criteria
- **CDF approval** — Initial data promising, **more data needed**
- **Rejection** — Safety or efficacy data fails to meet criteria

≤ 2 years

NICE re-evaluation

- **Approval**
- **Rejection**

DETERMINE PATHWAY

***Less data required** due Bayesian approach and precise patient stratification*

DETERMINE trial arm — **N = ~30**

DCB rate <10% → **Recruitment stops, trial arm closed**

DCB rate >30% →

CDF approval
Initial data promising, **real world data collected**

NICE submission

- **Approval**
- **Rejection**

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Considerations

- More expensive to set up and run than most units anticipate and need core funding
- Resource intensive especially at the outset

Academic platform studies present a unique opportunity to accelerate finding new treatments for rare cancers

World class investigators nationally and internationally

infrastructure for genomic profiling of tumours nationally

capitalize on alignment of trials within PRIME-ROSE to accelerate building the knowledge base faster & more effectively

Collaboration and data sharing potentially will allow us to define predictive molecular signatures

Links to the payers with new bespoke routes for approval of new treatments

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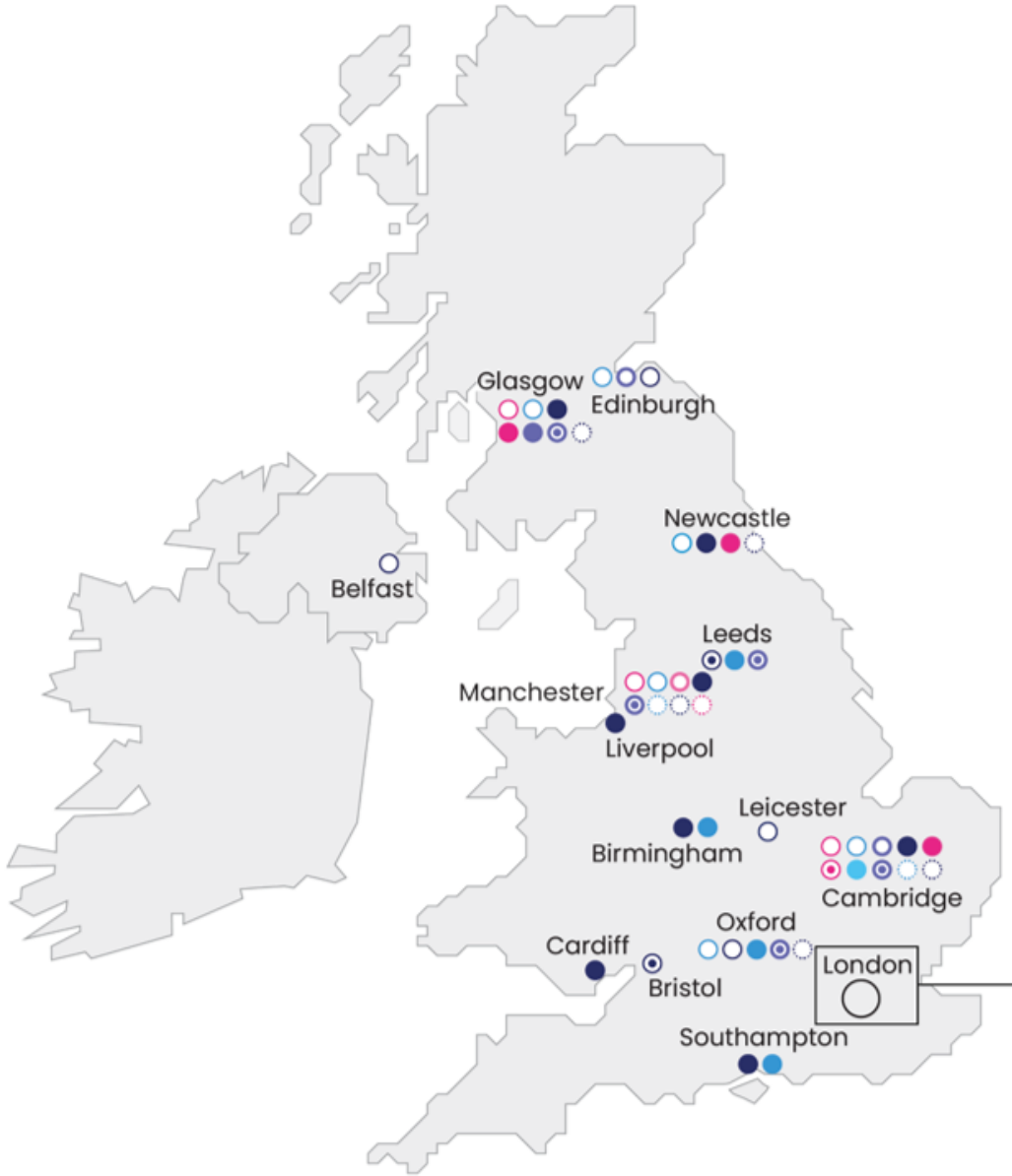

- Institutes (4)
- Centres (7)
- Lung Cancer Centre of Excellence (1)
- Brain Tumour Centre of Excellence (2)
- Experimental Cancer Medicine Centres (ECMCs) Adult and Paediatric (10)
- Experimental Cancer Medicine Centres (ECMCs) Adult (7)
- Experimental Cancer Medicine Centres (ECMCs) Paediatric (2)
- Clinical Trials Units (7)
- Cancer Research Horizons Drug Discovery Sites (4)
- Cancer Research Horizons-AstraZeneca Antibody Alliance Laboratory (1)
- Cancer Research Horizons-AstraZeneca Functional Genomics Centre (1)
- Manufacturing Facility (1)
- RadNet (7)
- International Alliance for Cancer Early Detection (ACED) (3)
- National Cancer Imaging Translational Accelerator (NCITA) (9)
- National Biomarker Centre (1)

London

Barts
- ECMC

CRUK City of London Centre (KCL, UCL, Barts, the Crick)
- Centre
- RadNet

CRUK Convergence Science Centre (ICR-Imperial)
- Centre

Imperial
- ECMC
- NCITA

Institute of Cancer Research
- Brain Tumour Centre of Excellence (joint with Cambridge)
- Clinical Trials Unit
- ECMC
- RadNet
- NCITA

King's College London
- NCITA

King's Health Partners
- ECMC

The Francis Crick Institute
- Institute
- Cancer Research Horizons Drug Discovery Site

Queen Mary University of London
- Clinical Trials Unit

UCL
- Lung Cancer Centre of Excellence (joint with Manchester)
- Brain Tumour Centre of Excellence (joint with Edinburgh)
- ECMC
- Clinical Trials Unit
- ACED
- NCITA

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