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CR UK & UCL Cancer Trials Centre:

Laura White –Trials Group Lead; Sharon Forsyth – Senior trials co-ordinator; Krystna Reczko, trials co-ordinator

NCRI National Cancer Research Institute

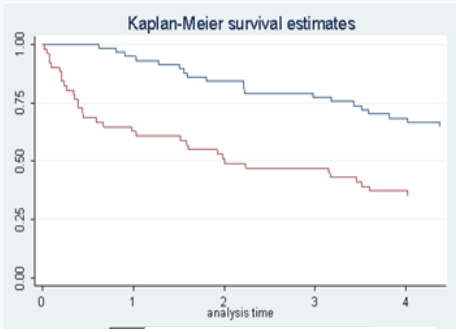
UCL

Cancer Research UK and UCL Cancer Trials Centre

Background and Rationale

- little change in treatment and outcome for osteosarcoma (OS) in recent years
- most clinical trials focused on young patients with resectable disease
- many groups of patients with poor prognosis, with no standard of care
- includes older patients, rare primary sites, metastatic disease
- no new agents ready for phase III / upfront studies

- only one phase I/II study in UK currently open specifically for patients with osteosarcoma



≤ 40 years

> 40 years

NCRAS 2011-2015

Recent sequencing and platform studies

- OS genome complex and heterogenous
- although some putative new targets, need validation

- Unmet need recognised by NCRI Sarcoma Clinical Studies Group
- Prioritised at Strategy day held in 2016

NCRI
National Cancer Research Institute

PURPOSE

The purpose of ICONIC is to deliver a step-change in the way we investigate better treatments and ways to improve outcome for OS by:

- forming a collaboration between clinicians, scientists, pathologists, radiologists, researchers and patient groups to work together in co-ordinated way across the UK

- recruiting **all newly-diagnosed patients** of **all ages across the UK** with longitudinal clinical data and tissue collection to form a prospective cohort to address clinical and biological questions

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PROTOCOL DEVELOPMENT

- involvement of co-investigators and collaborators across disciplines across UK
- involvement of a registered clinical trials unit (UCL Cancer Trials Centre) with statistical support
- patient and public involvement (PPI) from outset
- sample collection and analysis aligned to ongoing funded initiatives where possible to reduce costs, avoid duplication and maximise output
- aim to perform comparative analyses where possible for more robust validation in smaller numbers of patients

Cancer Research UK and
UCL Cancer Trials Centre

CLINICAL OBJECTIVES

- Determine **variation in management** of patients across the UK, including:
  - systemic therapy
  - surgery – determining operability; resection technique, complications
  - radiotherapy – indications and use
- particularly for those with poor prognosis including patients > 40 years, patients with less common primary sites, and unresectable or widely metastatic OS
- Use this information to develop new therapeutic protocols and improved management strategies for patients at risk

Sandra Strauss, Jeremy Whelan, Bernadette Brennan, Craig Gerrand, Kenny Rankin, Robin Young

BIOLOGICAL OBJECTIVES

- determine the impact of **intratumour heterogeneity and evolution** on treatment response and patient outcome[1]
- Identify novel genetic and immune **tumour biomarkers** through multi-platform analyses[1]
- correlate **molecular characteristics** with clinical outcomes to identify patients at higher risk and potentially identify **therapeutic targets**
- Evaluate two methodologies of Circulating Tumour Cell (CTC) isolation; and ctDNA profiling as **circulating biomarkers** to predict burden of disease, response to therapy and outcome[1,2]

1. Adrienne Flanagan

2. Kenny Rankin, Dominque Heymann, Robin Young

PATIENT EXPERIENCE

1. Patient-reported quality of life and functional outcome measures:

- validate a sarcoma–specific patient reported outcome measure (PROM)–sarcoma assessment method **(SAM)** as a longitudinal measure to detect changes in self-reported outcome over time
- compare with standard QoL measures : EORTC-Q30 and Global assessment score
- assess patient functional outcomes over time using TESS

Rachael Taylor, Craig Gerrand, Jeremy Whelan

PATIENT EXPERIENCE

2. Routes and time intervals to diagnosis:

- To identify and characterise timescales within the **diagnostic pathway** of patients with Osteosarcoma.
- To identify particular groups of patients at risk of prolonged/complex diagnostic routes.
- To prospectively identify outcomes associated with times/routes to diagnosis.
- To identify where interventions may be placed to improve the diagnostic experience for patients with osteosarcoma

Using methodology developed by International Cancer Bench Marking Partnership

- Questionnaires to patients, clinicians, and GPs

Lorna Fern, Jeremy Whelan

ICONIC

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Provide the infrastructure to create a platform

- to conduct therapeutic clinical trials and more rapidly investigate novel agents in specific populations
- investigate additional biomarkers including potential imaging biomarkers
- for further hypothesis-generation, and increased collaboration within the UK and internationally

- Initially funded for 4 years

→ 2 stages

ICONIC 1st Stage : feasibility and pilot studies – 2 years

Can we recruit patients with high quality clinical, imaging and longitudinal biospecimen collection to address objectives?

- clinical data capture
- surgical data – is this feasible across surgical centres
- imaging data - determine feasibility of establishing an imaging repository
- pathology infrastructure to support tissue collection across 5 bone tumour site – BCRT –can high quality tissue specimens and longitudinal blood samples be obtained for proposed analyses?
- patient experience questionnaires

Can we recruit across the UK?

- Across oncology and surgical centres
- Across England, Scotland, Wales and Northern Ireland
- Across adult and paediatric centres

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STAGE 1-pilot and aligned studies

Frozen tumour

High quality specimen collection → Whole genome sequencing (WGS), RNA seq , CAN, Epigenetic profiles, Neoantigens.

Lead: Professor Flanagan

- Aligns with ongoing funded projects: whole genome Sequencing: **100,000 Genome Project**
- RNA seq, proteomics, neo-antigens, bioinformatics
- Funded by **Tom Prince Trust**, **Osteosarcoma Research Consortium**
- **Aligns with BCRT biobanking strategy**
- Funding for ongoing tumour WGS through funding from NHS England

FFPE

Optimise DNA/RNA extraction for targeted genomic profiling, CN analysis, pilot targeted sequencing

Clinical data / imaging

PATIENT-diagnosis and treatment

- inform current practice and feasibility for clinical trials eg: > 40 years; **local therapy**
- establishment of an imaging repository

blood

Pilot study to evaluate **CTC** – isolation and characterisation Sample collection for **ctDNA**/ methylome profiling

Two methods : flow cytometry MT1-MMP **(Rankin)**
Parsortex/Deparray **(Young, Heymann)**
ctDNA profiling (Flanagan)

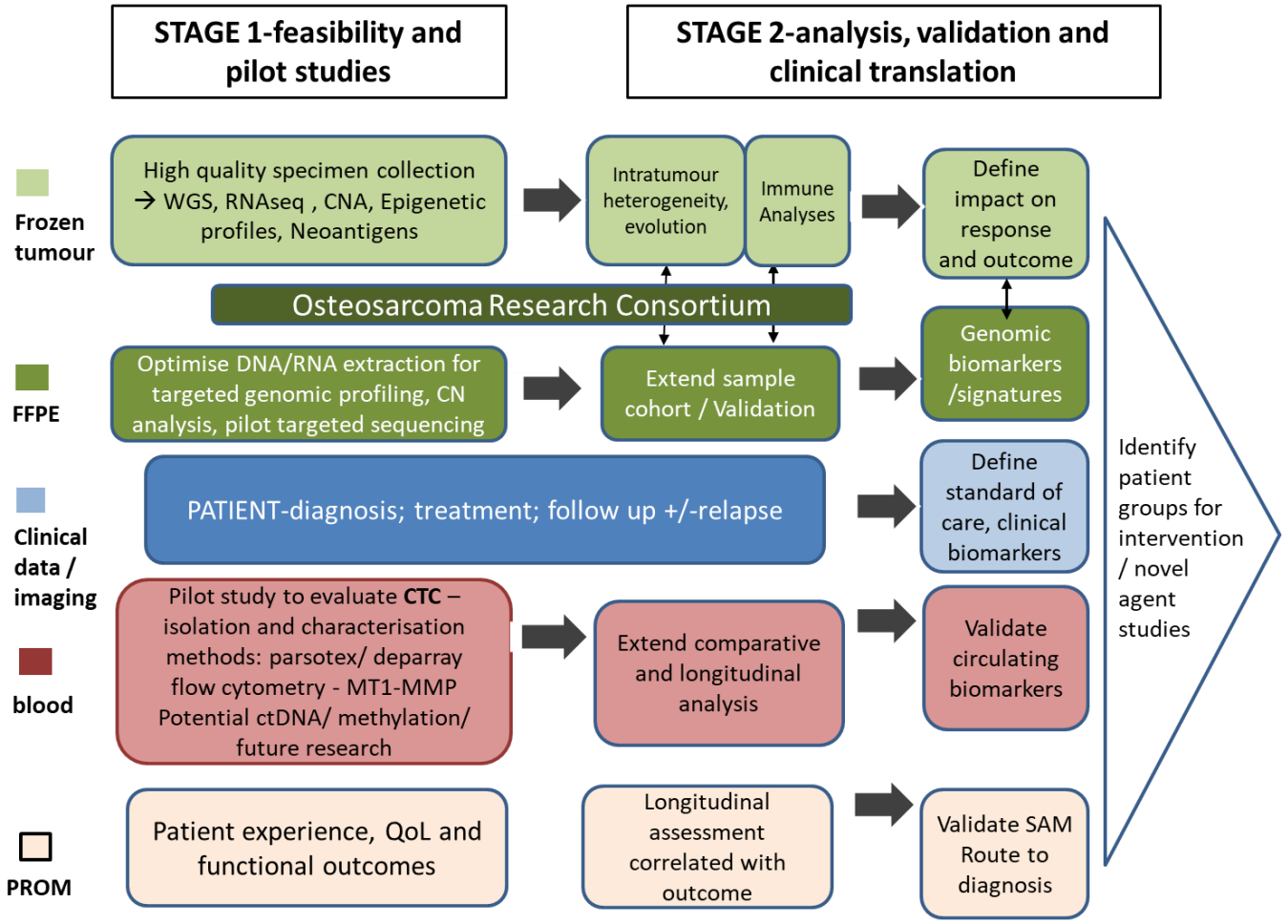
PROMs, Questionnaires

Patient experience, QoL and function

Validate SAM **(Taylor, Gerrand, Whelan)**
Routes and intervals to diagnosis **(Fern, Whelan)**

ICONIC SCHEMA

enrol ~ 200 patients over 3 years recruitment with ≥ 1 year follow up



(FFPE = fixed formalin paraffin-embedded; WGS= whole genome sequencing; CAN= copy number alterations, CTC = circulating tumour cell; PROMS = patient reported outcome measures, SAM = sarcoma assessment method)

maximising benefit for patients, clinicians and researchers

- platform for trials in high risk populations
- platform for additional companion studies: eg imaging biomarker studies
- platform for hypothesis-driven local control studies
- data to apply for additional funding to support further hypothesis-driven research
- repository / biobank of biological samples and paired clinical data for further interrogation by current and other study groups
- Opportunities for International collaboration

- Launch meeting: 26 February 2019

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