A biomarker enrichment trial of anti-EGFR agents in patients with advanced colorectal cancer (aCRC) with wild-type RAS and right primary tumour location (right-PTL)

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3 Trial Summary

Title	A biomarker enrichment trial of anti-EGFR agents in patients with advanced colorectal cancer (aCRC) with wild-type RAS and right primary tumour location (right-PTL)
Acronym	ARIEL
Background	The standard of care for fit patients with aCRC with a RAS-wt tumour is two cytotoxic drugs plus an anti-EGFR (epidermal growth factor receptor) agent, cetuximab or panitumumab (endorsed by NICE). However, meta-analysis of 6 randomised controlled trials (RCT) shows (a) that right-PTL confers a worse prognosis than left colon or rectal primary and (b) that anti-EGFR agents are ineffective in right-PTL RAS-wt patients. Reacting to these data, USA national guidance (NCCN) now stipulates that right-PTL patients should not receive anti-EGFR agents, but instead an anti-VEGF drug bevacizumab. In contrast, NICE continues to allow treatment of right-PTL patients with anti-EGFR agents and no alternative biological agent is available. Better patient selection for anti-EGFR agents with effective biomarkers is possible. Of many candidate predictive biomarkers, the most consistent data is for the EGFR ligands EREG and AREG, with high expression conferring sensitivity and low expression resistance. These findings have been validated in the large UK phase III trials PICCOLO and COIN. In PICCOLO a combined ligand and PTL analysis revealed that in right-PTL patients, high ligand expression was associated with marked panitumumab benefit; in right-PTL patients with low expression, chemotherapy plus panitumumab was significantly inferior to chemotherapy alone. It is likely that, rather than making treatment decisions on PTL alone, patient interests would be better served by integrating ligand assessment into routine care. However, more data is needed: EREG/AREG have to date been measured retrospectively; feasibility for delivery of results to sites must be demonstrated, and prospective confirmation is needed to confirm the benefit of EGFR therapy in patients with EREG/AREG-high, right-PTL cancer.
Population	Registration: Patients with advanced colorectal cancer (aCRC) with wild-type RAS or RAS unknown and right primary tumour location (right-PTL) Randomisation: Patients with advanced colorectal cancer (aCRC) with wild-type RAS and right primary tumour location (right-PTL) and high EREG/AREG
Design	Multi-centre, phase IV, open label, randomised controlled biomarker enrichment trial with an internal pilot phase
Objectives	**Primary:** To determine whether first-line chemotherapy with cetuximab or panitumumab is more effective than chemotherapy alone in achieving early tumour shrinkage (ETS) after 8 weeks of treatment in randomised patients. **Secondary:** 1. To assess the effectiveness of first-line chemotherapy with cetuximab or panitumumab compared to chemotherapy alone on: a. Depth of response at 16 weeks, i.e. the maximum tumour shrinkage observed in a patient compared with baseline b. Overall survival c. Overall Treatment Utility, assessed at 8 weeks (measured by patient or doctor response to questions around treatment allocation, scored as good intermediate or poor) d. Patient-reported HRQOL (as measured by EORTC QLQ-C30 and EORTC QLQ-CR29 with additional items to cover anti-EGFR symptomatic toxicity using the EORTC-QLQ item library) assessed at randomisation, 8 weeks, 16 weeks and 12 months

	2. To assess the cost-effectiveness of using anti-EGFR agents in addition to first-line chemotherapy compared to chemotherapy alone, assessed by cost-per incremental quality adjusted life-year over a lifetime. 3. To evaluate the patient acceptability to the trial procedures, assessed by looking at reasons for patients refusing consent to registration and reasons for patients refusing consent to go through randomisation after consenting to registration. 4. To evaluate toxicity.
Intervention	Participants who are EREG/AREG high will be randomised to receive: • Standard chemotherapy alone or • Standard chemotherapy plus cetuximab or panitumumab.
Sample size	The ARIEL trial aims to randomise 162 patients over a 3 year period. Given the biomarker prevalence we estimate that we will need to register 440 patients to identify sufficient RAS-wt patients with high tumour EREG/AREG levels.
Follow-up	All patients will be followed up to one-year post-randomisation as a minimum with a final assessment in all patients when the last patient has completed a year of follow up – median 3.5 years follow up.
Primary endpoints	Early tumour shrinkage (ETS), measured 8 weeks after the start of treatment
Secondary endpoints	• Depth of response at 16 weeks from start of treatment • Overall Treatment Utility (OTU), assessed at 8 weeks from start of treatment. • Overall survival (OS) • Patient-reported HRQOL • Cost effectiveness • Toxicity
Exploratory endpoint for translational research	• Assessment of prognostic and predictive ability of other candidate biomarkers with regard to patient outcomes and anti-EGFR efficacy, including negative hyperselection by gene alterations in circulating tumour DNA (ctDNA) related to primary resistance to anti-EGFR therapy

Figure 1: Trial Schema

Registration Phase

Registration (N=440)

- Potentially eligible patients (right PTL aCRC; RAS-wt or RAS status unknown; anti-EGFR-naïve) approached at initial oncology consultation
- Consent obtained for registration and biomarker analysis

Biomarker testing

- **If RAS status unknown:** local testing OR tumour material transferred to central laboratory in Leeds for RAS/BRAF testing
- **RAS-wt patients (N=324):** tumour material transferred to Birmingham for EREG/AREG testing
- **RAS-mut patients:** no further participation

EREG/AREG-LOW

- Treated off study – standard of care
- Data collection at 1 year

RAS-wt and EREG/AREG-HIGH - Eligibility & Baseline Assessment

- Invited to participate in the study
- **Inclusion criteria:** Aged ≥ 18 years, confirmed right PTL aCRC, RAS-wt, EREG/AREG-high, BRAF status known; RECIST assessable aCRC, fit for combination chemotherapy plus cetuximab/panitumumab, medically fit for trial treatment
- **Exclusion criteria:** Prior chemotherapy for aCRC, prior treatment with anti-EGFR, received >1 cycle of chemotherapy since registration
- **Baseline CT scan:** within 28 days prior to randomisation up 7 days after randomisation
- Consent for main trial obtained from eligible patients

Randomisation Phase

Randomisation (N=162)

Chemotherapy + cetuximab/panitumumab (N = 81)

Chemotherapy alone (N = 81)

- Minimisation on a 1:1 basis incorporating a random element incorporating following stratification factors:
  - Choice of first-line chemotherapy (irinotecan; oxaliplatin-based; other)
  - Tumour location (transverse; caecum; ascending)
  - Prior adjuvant or neoadjuvant chemotherapy (yes; no)
  - Primary tumour resected (yes; no)

Treatment & Assessment

- Commence oxaliplatin or irinotecan based doublet chemotherapy +/- cetuximab or panitumumab in accordance with local practice
- CT scan at 8 weeks to determine early tumour shrinkage (primary outcome)
- CT scan at 16 weeks to determine depth of response at 16 weeks
- Data collection at: baseline, 8 weeks, 16 weeks, 12 months, and then 12 months after recruitment of last patient

Outcomes

To assess the following for chemotherapy with anti-EGFR agents compared to chemotherapy alone:

- Primary endpoint: early tumour shrinkage at 8 weeks
- Secondary endpoints:
  - Depth of response at 16 weeks
  - Overall survival (OS)
  - Overall Treatment Utility (OTU)
  - Cost-effectiveness
  - Patient reported health-related Quality of life
  - Patient acceptability
  - Toxicity

4 Abbreviations

Abbreviation	Definition
5FU	5-fluorouracil
aCRC	Advanced colorectal cancer
AE	Adverse event
ALT	Alanine aminotransferase
AR	Adverse reaction
AREG	Amphiregulin
AST	Aspartate aminotransferase
BRAF	A human gene that encodes a protein called B-Raf
BRAF-mut	BRAF mutant
BRAF-wt	BRAF wild type
CEA	Carcinoembryonic antigen
CI	Chief investigator
CLIA	Clinical Laboratory Improvement Amendments
CMS	Consensus molecular subtype
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Central Portfolio Management System
CRF	Case report form
CT	Computerised tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
CTRU	Clinical Trials Research Unit
CV	Curriculum vitae
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucleic acid
DpR	Depth of response
DSUR	Development Safety Update Report
DPYD	Dihydropyrimidine Dehydrogenase
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
EMC	Electronic Medicines Compendium
EME	Efficacy and Mechanism Evaluation
EORTC	European Organisation for Research and Treatment of Cancer
EREG	Epiregulin
ETS	Early tumour shrinkage
EudraCT	European Clinical Trials Database

FBC	Full Blood Count
FFPE	Formalin-fixed paraffin-embedded
FOLFIRI	5-fluorouracil, folinic acid and irinotecan
FOLFOX	5-fluorouracil, folinic acid and oxaliplatin
FOLFOXIRI	5FU, folinic acid, oxaliplatin and irinotecan
GCP	Good clinical practice
GFR	Glomerular filtration rate
GLH	Genomic Laboratory Hubs
HEAP	Health economic analysis plan
HR	Hazard ratio
HRA	Health Research Authority
HRQOL	Health related quality of life
HTA	Human Tissue Authority
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IMP	Investigational medicinal product
IRAS	Integrated Research Application System
IrMdG	5-fluorouracil, folinic acid and irinotecan
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
IV	Intravenous
JiT	Just-in Time
KM	Kaplan-Meier
LFTs	Liver function tests
LoS	Length of stay
MAR	Missing at random
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next generation sequencing
NHS	National Health Service
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ORR	Overall response rate
OS	Overall survival

OTU	Overall treatment utility
OxMdG	5-fluorouracil, folinic acid and oxaliplatin
PFS	Progression-free survival
PI	Principal investigator
PICC	Peripherally inserted central catheter
PIN	Personal identification number
PIS	Patient information sheet
PP	Per-protocol
PPI	Patient and public involvement
PROs	Patient-reported outcomes
PS	Performance status
PTL	Primary tumour location
QA	Quality assurance
QALY	Quality-adjusted life year
QoL	Quality of life
RAS	A family of genes that include KRAS and NRAS
RAS-wt	RAS wild type
RCT	Randomised controlled trial
REC	Research ethics committee
RECIST	Response Evaluation Criteria In Solid Tumours
RNA	Ribonucleic acid
RSI	Reference safety information
RT-PCR	Reverse transcriptase polymerase chain reaction
RT-QPCR	Quantitative reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SMD	Sum of maximum diameters
SoC	Standard of care
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial management group
TSC	Trial steering committee
U&Es	Urea and electrolytes
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation
wt	Wild type

5 Introduction

5.1 Background

Around 42,000 people in the UK develop colorectal cancer each year, and over a third of these will eventually die with advanced disease. The mainstay of treatment for advanced colorectal cancer (aCRC) is palliative chemotherapy, sometimes with the addition of a therapeutic antibody targeting epidermal growth factor receptor (EGFR).

About half of aCRC patients' tumours are free of activating mutation in the RAS oncogenes (RAS-wt), and these patients are eligible under NICE guideline (TA439) for first-line combination anti-EGFR (cetuximab or panitumumab) with doublet chemotherapy (a fluoropyrimidine with either irinotecan or oxaliplatin). The randomised controlled trials (RCTs) which established anti-EGFR drugs also showed that among RAS-wt patients there is wide variability of response ranging from marked benefit to negative effects, so refinement of patient selection is of crucial importance to avoid both patient harm and wasted resources.

The right and left colon have distinct embryological origins and their tumours differ in their prevalent molecular characteristics. Right-sided primary tumour location (right-PTL) carries a generally worse prognosis.[1-3] In addition, retrospective subgroup analyses from "+/- anti-EGFR' trials show that primary tumour location (PTL) is a potential predictive marker for anti-EGFR therapy: right-PTL being associated with reduced or absent benefit and left-PTL with increased benefit.[4] On the basis of these subgroup analyses, USA guidelines (NCCN) have been amended to include the use of PTL in patient selection for anti-EGFR therapy.[5] However, this approach is not universal and the drug licenses and NICE guidance do not recognise PTL. There is a lack of high-quality data and, in particular, an understanding of which molecular differences are driving the clinical observations.

5.2 Existing Evidence

5.2.1 Prediction of benefit for anti-EGFR agents

Early in clinical development of anti-EGFR agents it was apparent that a sizable proportion of patients do not respond. It was established early on that an activating mutation in KRAS or NRAS is a negative predictive biomarker: patients with these mutations will not benefit and may be harmed.[6] The drug licences were therefore amended to limit their use to RAS-wt patients.

However, not all patients with RAS-wt aCRC benefit from anti-EGFR therapy, and additional predictive biomarkers are needed to identify likely responders and non-responders within the RAS-wt population. BRAF-mut occurs in 7-9% aCRC and is associated with worse prognosis. Retrospective studies have given conflicting information about whether BRAF-mut predicts resistance, so current drug licences and national guidance do not exclude BRAF-mut patients from anti-EGFR therapies. Other candidate predictive biomarkers include EGFR ligands[7] (discussed below), HER2 amplification,[8] HER3 overexpression,[9] Consensus Molecular Subtype (CMS) mRNA expression profile[10] and miR-31-3p.[11]

5.2.2 Primary tumour location (PTL)

Overall, right-PTL cancer has a worse prognosis, and PTL may also influence response to specific treatments.[1-3] It is important to recognise, however, that differences in prognosis or response are likely to be related to the underlying molecular alterations for which PTL is acting as a surrogate.

With that proviso, a recent pooled analysis of 6 RCTs found right-PTL to be associated with reduced or lack of benefit from anti-EGFR agents.[12] This has led to changes in practice but these are inconsistent and relate to the availability of alternative options. USA guidance (NCCN) has been amended to recommend first-line treatment of RAS-wt, right-PTL patients with anti-VEGF in preference to anti-EGFR therapy; however, anti-EGFR therapy can still be used as a later-line option. In contrast, in the UK, anti-VEGF therapy is not available and anti-EGFR drugs are restricted to first-line use; UK oncologists must therefore decide between offering anti-EGFR therapy first-line or not at all.

5.2.3 Epiregulin and Amphiregulin as biomarkers for anti-EGFR efficacy

There is good evidence that upregulated expression of the EGFR ligands epiregulin (EREG) and/or amphiregulin (AREG) is predictive for anti-EGFR agent efficacy.[7, 13-17] Following strong signals in several retrospective series, clinical validation was demonstrated in a large phase III randomized trial (PICCOLO: irinotecan/panitumumab [IrPan] vs irinotecan for second-line treatment of KRAS-wt aCRC).[18]

PICCOLO used a prospectively-designed model in which the impact of panitumumab was compared in patients with high expression of either ligand versus those with neither. In patients with high expression panitumumab produced marked improvement in progression-free survival (PFS), while patients with low expression gained no benefit (Figure 2). There was no significant prognostic effect. EREG/AREG effect was independent of *BRAF*-mutation status.[18]

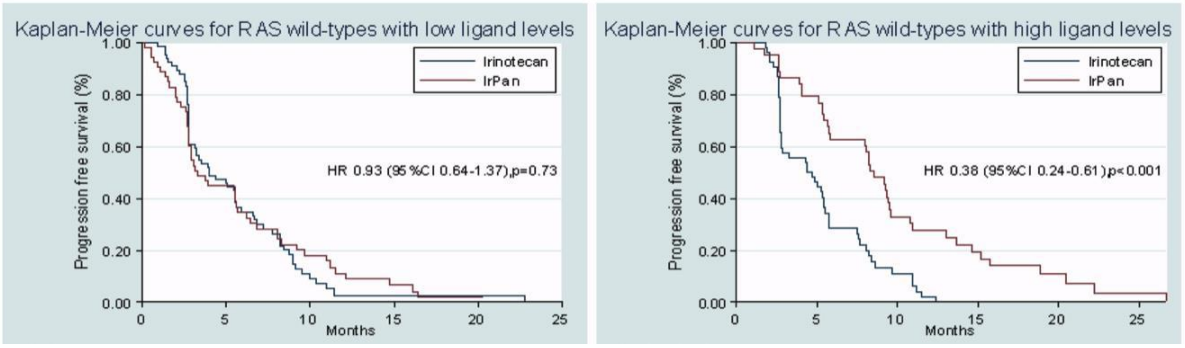


Figure 2: KM curves for IrPan vs Ir in patients with low ligand levels, then patients with high ligand levels (interaction p=0.001)

Similar results were seen in COIN, a phase III UK based RCT in which patients were allocated to first-line oxaliplatin and 5FU +/- cetuximab.[19] RAS-wt patients were assessed for EREG/AREG status using CLIA compliant laboratories (Almac). As in PICCOLO, RAS-wt patients with high ligand expression had significant benefit from cetuximab (PFS HR 0.46 [p=0.004]); while those with low expression had no benefit (HR=0.90 [p=0.62]). After adjustment for BRAF, PTL and performance status, these remained significant.[20] A similar

result is observed for the OS outcome: adjusted HR = 0.44 (p=0.008) vs 1.15 (p=0.53); interaction p=0.015.

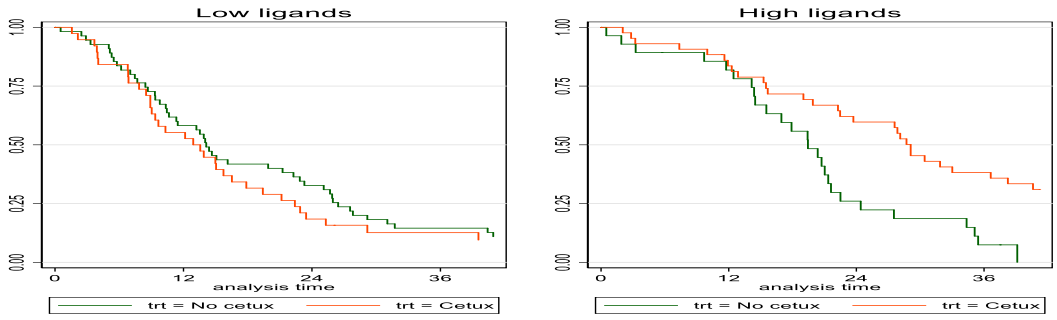


Figure 3: PFS with OxFU+cetuximab vs OxFU alone in patients with low or high ligand expression (interaction p=0.001)

Further evidence comes from a third line trial (CO.17, Cetuximab vs best supportive care in KRAS-wt aCRC); in this trial, only EREG was tested, but once again patients with high expression gained significant benefit from cetuximab in terms of PFS and OS, while those with low expression did not.[21]

5.2.4 Proof of concept: interaction between EREG/AREG and PTL

The evidence summarised above shows that in RAS-wt aCRC:

a) Benefit from anti-EGFR therapy is associated with PTL, with minimal or no overall benefit seen in patients with right-PTL cancers
b) Benefit from anti-EGFR therapy is strongly associated with high EGFR ligand expression

It is therefore important to consider the 50% patients with right-PTL cancer who also have high EREG/AREG expression. Using PICCOLO data, a combined PTL and EREG/AREG analysis was performed. This shows that EREG/AREG is an independent predictor of panitumumab PFS benefit: patients with right-PTL but high EREG/AREG expression had marked PFS benefit with IrPan compared with irinotecan (HR=0.20 [0.05-0.91], p=0.04); those with low EREG/AREG did not (HR=1.23 [0.72-2.11], p=0.45). Treated as continuous biomarkers, EREG and AREG were independent predictors of panitumumab effect independent of PTL.

Thus within the right-PTL population, ligand expression may identify 50% patients who would benefit, but from whom anti-EGFR therapy is withheld if the treatment decision is based on PTL. Conversely ligand expression may identify 50% patients who will not benefit and may be harmed by anti-EGFR therapy if treated in accordance with current NICE guidelines.

5.3 Rationale for this study

In the UK anti-EGFR agents are only funded for first-line treatment, no alternative biological agent (e.g. anti-VEGF) is available and overall outcomes for right-PTL patients are poor. However, anti-EGFR therapy incurs significant toxicity and cost, and should clearly not be used for patients who will not benefit or may even be harmed. In a survey of 43 UK oncologists, the large majority reported using anti-EGFR therapy in RAS-wt patients with left-PTL, but for right-PTL patients there was no agreement: 32% would routinely use an anti-EGFR drug. This highlights that there is no agreed ‘Standard of Care’ (SoC) in right-PTL patients.

EGFR therapy decisions based either purely on RAS status, or on RAS status and PTL, risk harming patients through over-treatment or withholding potentially beneficial therapy. It is likely that, rather than making treatment decisions on PTL alone, patient interests would be better served by integrating ligand assessment into routine care. However, more data is needed: EREG/AREG have to date been measured retrospectively; feasibility for delivery of results to sites must be demonstrated, and prospective confirmation is needed to confirm the benefit of EGFR therapy in patients with EREG/AREG-high, right-PTL cancer.

For EREG/AREG as a predictive biomarker to impact drug licenses, national guidance and routine practice requires prospective testing in this trial, which will provide both biomarker validation and a model for delivery. The current level of evidence from sub-group analyses of RCTs is insufficient. Demonstrating the validity and utility of EREG/AREG ligands in right-PTL aCRC will fill this knowledge gap and potentially impact practice internationally for patient benefit.

5.4 Translational research

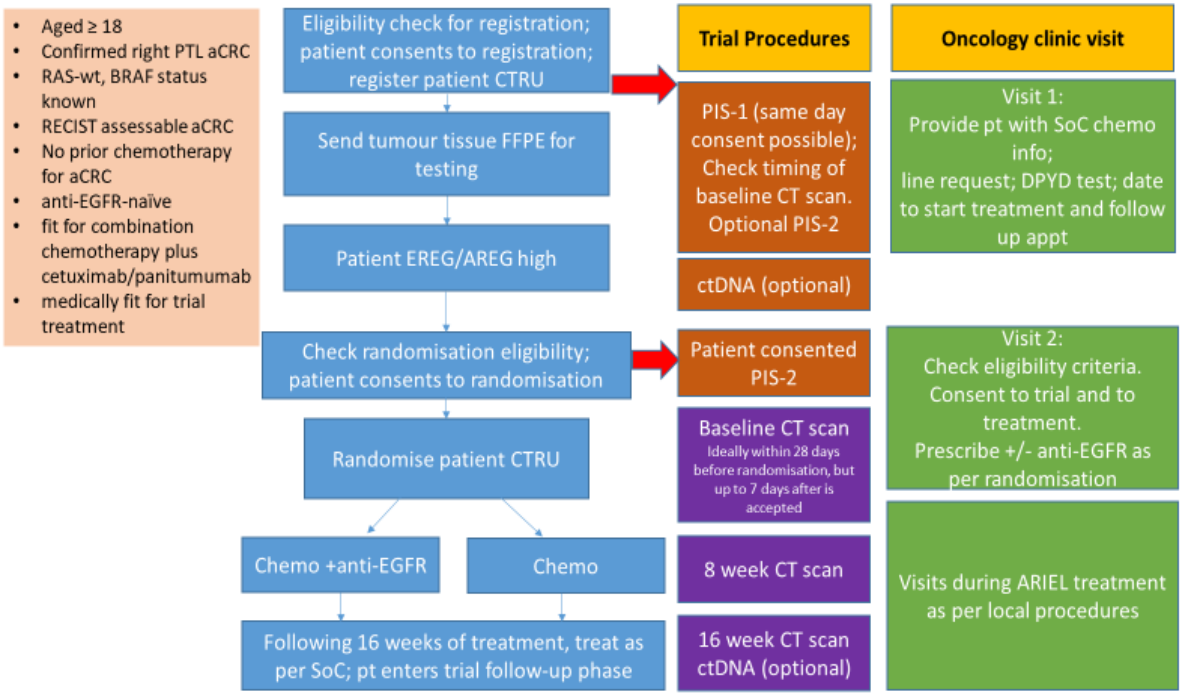
As well as meeting an unmet clinical need, this study will be translationally rich. There is a pressing need for further data to clarify the role of BRAF status, and our work in PICCOLO has already demonstrated that HER3 expression may provide further refinement of the predictive information from EREG/AREG. The planned DNA and RNA analyses will generate additional ‘free’ data (e.g. from RNAseq) allowing other candidates and targets to be explored. ctDNA collection at registration and on completion of the trial treatment period will enable evaluation of any synergistic predictive effect of negative hyperselection by gene alterations in ctDNA related to primary resistance to anti-EGFR therapy([22] [23] [24] and provide a resource for future study of acquired resistance.

6 Trial Overview

The ARIEL study has 2 phases registration and randomisation (the main trial). Within the registration phase, patients will be identified for the study if they have aCRC with a right-PTL and tumour samples shall be sent for biomarker assessment. Sites will be informed of the results and whether the patient is eligible for randomisation. Within the randomisation phase, patients will be randomised to study treatment. These phases are described separately within the protocol.

This protocol is pragmatic regarding the patient flow through registration and randomisation at individual sites. We assume that patients will need at least one face-to-face appointment, some centres will offer two visits in this situation. However, we acknowledge the increased use of virtual consultations and have suggested some modifications of the pathway to facilitate this. The patient flow and procedures are shown in Figure 4 below:

Figure 4. Patient flow and procedures



Within this particular clinical pathway patients often have their first clinical review without complete molecular information (e.g., RAS, BRAF (or MSI) status outstanding). We would therefore encourage sites to consider their ARIEL pathway based upon this clinical scenario.

We recommend that patients are either:

- Given both the registration and the randomisation PISs at the initial visit, at the point of ARIEL registration.
- Or, following AREG/EREG testing, patients who are eligible are contacted by the Research Nurse who will email or post the randomisation PIS so that the patient has the opportunity to consider the trial prior to their next consultation.

For registration phase – GO TO SECTION 11

For randomisation phase – GO TO SECTION 12

7 Aims and Objectives

7.1 Aims

The aim of the trial is to assess the feasibility of EREG/AREG assessment as a clinical diagnostic standard, used to guide clinical decision making in right-PTL, RAS-wt aCRC. Further to this, the aim is to determine whether EREG/AREG status identifies right-PTL patients who will benefit from the addition of anti-EGFR therapy to first-line chemotherapy. The trial will also assess survival, cost-effectiveness, quality of life (QoL) and Overall Treatment Utility (OTU) for the patients that undergo randomisation.

7.2 Primary objective

To determine whether first-line chemotherapy with cetuximab or panitumumab is more effective than chemotherapy alone in achieving early tumour shrinkage (ETS) after 8 weeks of treatment in patients who are EREG/AREG positive.

7.3 Secondary objectives

1. To assess the effectiveness of first-line chemotherapy with cetuximab or panitumumab compared to chemotherapy alone on:
    a. Depth of response at 16 weeks from start of treatment, i.e. the maximum tumour shrinkage observed in a patient compared with baseline
    b. Overall survival
    c. Overall Treatment Utility, assessed at 8 weeks from start of treatment (measured by patient or doctor response to questions around treatment allocation, scored as good, intermediate or poor)
    d. Patient-reported HRQOL (as measured by EORTC QLQ-C30 and EORTC QLQ-CR29 with additional items to cover anti-EGFR symptomatic toxicity using the EORTC-QLQ item library) assessed at randomisation, 8 weeks, 16 weeks and 12 months.
    e. Frequency and intensity of toxicity events
2. To assess the cost-effectiveness of using anti-EGFR agents in addition to first-line chemotherapy compared to chemotherapy alone, assessed by cost-per incremental quality adjusted life-year over a lifetime.
3. To evaluate the patient acceptability to the trial procedures, assessed by looking at reasons for patients refusing consent to registration and reasons for patients refusing consent to go through randomisation after consenting to registration.

8 Design

ARIEL is a multi-centre, phase IV, open label, randomised controlled biomarker enrichment trial with an internal pilot phase which plans to recruit a total of 162 participants for randomisation. This trial will assess whether in RAS-wt patients with right-PTL aCRC, stratification by EREG/AREG status identifies patients who benefit from the addition of anti-EGFR agent to chemotherapy, and will test the feasibility of delivering EREG/AREG for routine clinical decision making. Patients will be assessed for EREG/AREG (high vs low at the 40th centile of expression). EREG/AREG low patients will not be randomised but will be followed up in a separate group of ~162 patients. Recruitment is to occur over a 3 year period with a further minimum 12 months for follow-up.

Participants will be randomised via minimisation in a 1:1 ratio to receive either anti-EGFR agent in addition to chemotherapy or chemotherapy alone.

The ARIEL study period is the first 16 weeks of chemotherapy, up to and including the 16 week scan. However, we shall continue to collect details on subsequent treatment beyond 16 weeks. Minimisation factors are detailed in Section 12.7.

Further details around the intervention treatment products and their administration to participants are given in Section 14.

8.1 Outcome measures

8.1.1 Internal Pilot

In order to assess the feasibility and design assumptions, the trial includes an internal pilot phase, split into three stages:

- *Stage 1* will assess the time to return of the biomarker results of the patients and whether testing can feasibly be integrated into the clinical care pathway. This will be assessed once 20 patients are registered or after 6 months of recruitment (whichever is later) and if seen to be infeasible, will cause the trial to close to recruitment.
- *Stage 2* will assess recruitment rate and assumptions made regarding the biomarkers for the study sample size and will change trial design if the proportion of patients with a particular biomarker status is different to design assumptions. The number of patients randomised in the first 18 months will be taken and assessed against a Red/Amber/Green (Stop/Continue with changes/Continue as is) decision cut-point to decide on future conduct of the trial.
- *Stage 3* will run to completion and provide evidence with respect to the treatment comparison in the biomarker positive group.

8.1.1.1 Stage 2 Recruitment Feasibility

To confirm feasibility of recruitment, recruitment from all sites within the first 18 months of the trial opening will be assessed, with analysis and decisions about stop/continue made. ‘Red/Amber/Green’ targets for recruitment within the first 18 months have been set, where reaching the ‘Green’ target should allow the targeted sample to be reached within 3 years; reaching the ‘Amber’ target should allow the target sample size to be reached within

approximately 3 years, with modifications to trial procedures; and a 'Red' target indicates the trial will not be able to recruit the amount of patients required in an acceptable timeframe, and that a decision about stopping is required.

The 'Green' target is set at randomising ≥53 of the target of 162 patients within the first 18 months of the tria The 'Amber' target is set at randomising 40-52 patients within 18 months. If <40 patients are randomised, this will be graded as 'Red' and the trial will undergo a stopping decision. This decision will be made by the TSC and the funder.

If the 'Amber' target is reached, potential modifications will be considered in discussion with the DMEC, TSC and the funder, including opening additional UK sites, further trial publicity or potential adjustment to the eligibility criteria.

8.1.2 Outcome measures for comparison in the biomarker positive group

The participants who are EREG/AREG high will be randomised into either the anti-EGFR plus chemotherapy or chemotherapy alone arm. These treatment arms will be compared for the following in the intention to treat (ITT) and per-protocol (PP) populations (defined in Section 22):

Primary Outcome

- Early tumour shrinkage (ETS) measured at 8 weeks

Secondary Outcomes

- Depth of response at 16 weeks
- Overall Treatment Utility (OTU)
- Overall survival (OS)
- Cost-effectiveness
- Patient-reported health-related QOL (HRQOL)
- Patient acceptability
- Toxicity

9 Participating Sites and Investigators

9.1 Participating sites

Each participating site must be able to comply with the following, as applicable to the trial activities taking place at the site:

- Collection, preparation and shipment of biological samples, trial treatments, imaging, clinical care, follow-up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research and amendments
- Data collection requirements, including adherence to CRF submission timelines as per Section 15
- Collection, preparation and shipment of biological samples for translational research
- Monitoring requirements as outlined in Section 23

Participating sites will be required to complete a trial-specific feasibility questionnaire to confirm that they have adequate resources and experience to conduct the study.

Approximately 40 sites will participate. It is anticipated that approximately 10 sites be set-up under the NIHR Just-in Time (JiT) activation scheme where site activation occurs rapidly, triggered in response to a potential research subject.

9.2 Principal Investigators and co-investigators

Sites must have an appropriate Principal Investigator (PI) authorised by the site to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. Investigators involved in the treatment and care of patients must be medical doctors and have experience of treating colorectal cancer. The trial will be registered with the NIHR Associate PI scheme and junior doctors are encouraged to apply to become an Associate PI for ARIEL (https://www.nihr.ac.uk/documents/associate-principal-investigator-pi-scheme/25040).

9.3 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site authorised personnel log.

CVs for all staff must be kept up-to-date, signed and dated and copies (or statement of their location) held in the Investigator Site File (ISF) held at site. An up-to-date, signed copy of the CV for the PI must be forwarded to the CTRU prior to site activation.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials. Evidence of current GCP training for the PI must be forwarded to the CTRU prior to site activation.

9.4 Site initiation

Before a site is activated, the CTRU trial team will arrange a site initiation with the site which, as a minimum the PI, pharmacy lead and research nurse must participate. The site will be trained in the day-to-day management of the trial. Site initiation will be performed by tele/video conference or via the provision of pre-recorded training material which staff will be required to watch and log on the trial authorised personnel log. Any queries or questions arising from the training material can be addressed by email (ARIEL@leeds.ac.uk) or a call can be arranged between the site and CTRU.

9.5 Essential documentation

With the exception of sites recruited through the NIHR JiT Scheme, the following documentation must be submitted by the site to the CTRU prior to site activation:

- Trial specific site feasibility questionnaire (identifying relevant local staff)
- All relevant institutional approvals (e.g. local NHS permission)
- A completed authorised personnel log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- A completed pharmacy authorised personnel log that is initialled and dated by the lead pharmacist
- A copy of the PI's current CV that is signed and dated
- A copy of PI's current GCP training certificate
- Signed PI declaration
- Signed lead pharmacist declaration
- A signed Clinical Trial Site Agreement (model Non-commercial Agreement for UK sites) between the Sponsor and the relevant institution, incorporating a Material Transfer Agreement

Sites must inform the CTRU of any additional sites involved in the patient pathway. Recruiting sites which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

9.6 Site activation

Once the CTRU trial team has received all the required essential documentation, the site has received their investigator and pharmacy site files and the site has been initiated, a site activation email will be issued to the PI and other research staff by CTRU. **Sites, including those recruited through the NIHR JiT Scheme, must not approach any potential patients until they have received an activation email from CTRU.**

10 Overview of patient screening and informed consent process

The process for giving information to patients about this study has a staged approach to reduce the possibility of information overload. A two-step process has been designed with plenty of time for consideration. The processes are summarised in Figure 5.

1. PIS-1 contains information about the nature of the research being considered and the need for further analyses of tumour tissue, with consent for release of an archival tumour block for molecular analyses. This will usually be given at the first consultation with the oncologist when the diagnosis of advanced or metastatic disease has been discussed.

   The patient can note any questions that they have, and to serve as a reminder to discuss them with the oncologist at their next appointment. Therefore, this first PIS is as simple and minimal as possible, whilst providing sufficient information for the patient to give informed consent for registration and release of the tumour block. Once written consent for registration, and eligibility has been confirmed (through completion of the Registration Eligibility Checklist), the patient is registered with the Leeds CTRU and a unique registration number is allocated to that patient.

2. PIS-2 contains standard clinical trial information on randomised controlled trials, general issues regarding possible unwanted side-effects and toxicity from treatment and further details of the potential advantages and disadvantages of the arms between which the patient will be randomised. PIS-2 can be provided when considered appropriate for the individual patient, e.g. with PIS-1, but must be provided in a timely fashion prior to final consent and randomisation with the biomarker panel results

10.1 Principles of informed consent

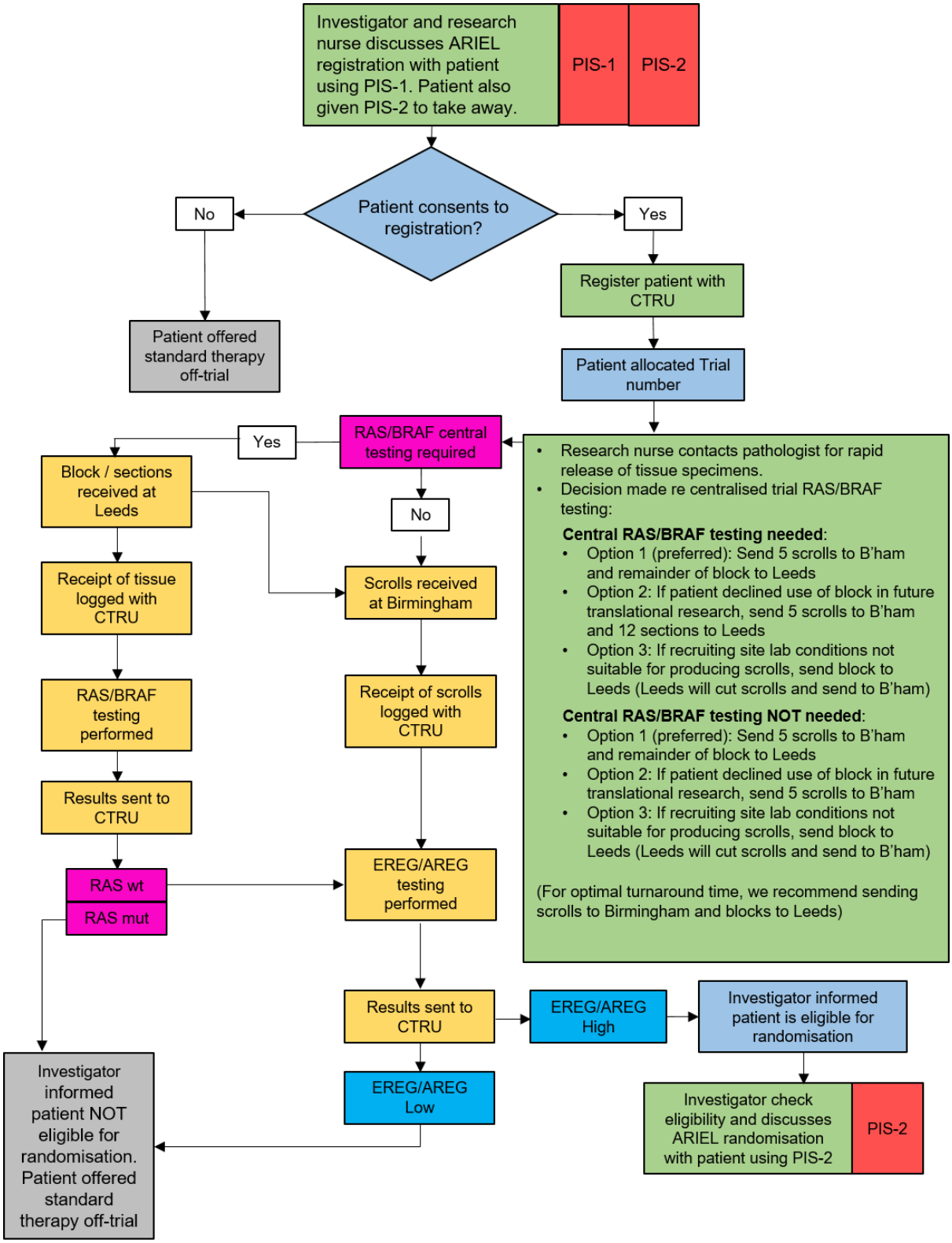
The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site. The PI must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised on the ARIEL authorised personnel log, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

The right of the patient to refuse consent without giving reasons will be respected. Further, participants will be told that they remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

Informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial which are out-with standard routine care at the participating site.

Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

Figure 5: Overview of the biomarker testing and 2 stage consent process (registration and randomisation)



11 REGISTRATION STAGE

11.1 Patient Selection for Registration

The ARIEL trial aims to randomise 162 patients over a 3 year period. Given the biomarker prevalence we estimate that we will need to register 440 patients to identify sufficient RAS-wt patients with high tumour EREG/AREG levels.

11.2 Recruitment setting

Patients will be recruited from oncology out-patient clinics, ideally at their first oncology appointment.

11.3 Baseline Molecular Status for Registration

Patients do not require an additional biopsy for ARIEL registration; archival tissue is acceptable.

Patients can be registered if they have **RAS-wt** tumours as assessed locally; tumour samples should be wild-type for KRAS codon 12/13/59/61/117/146 AND NRAS codon 12/13/59/61 (by pyrosequencing or NGS panel). If alternative technologies are used, the technology and sensitivity should be confirmed with the trial team (ARIEL@leeds.ac.uk).

The ARIEL trial has a provision for central RAS and BRAF testing if local testing pathways are likely to result in delays in the registration pathway (i.e. central testing within NHSE Genomic Laboratory Hubs). Therefore patients can be registered if their tumour **RAS status is unknown**.

Patients may be registered if they are either BRAF-wt or BRAF-mut, or if BRAF status is unknown. EREG/AREG will be centrally tested in all requested patients.

The anticipated turnaround for biomarker status is 7-10 days, in keeping with turnaround times for chemotherapy treatment and DPYD mutation testing.

11.4 Eligibility for registration

Patients meeting all of the inclusion criteria, and none of the exclusion criteria, will be considered for trial eligibility and biomarker analysis. Eligibility waivers to any of the inclusion and exclusion criteria are not permitted.

11.4.1 Inclusion criteria for registration

- Age ≥18 years
- Biopsy-confirmed[1] adenocarcinoma[2] of the colon with a right primary tumour location **(defined as proximal to and including the splenic flexure)[3]**

[1] Biopsy of metastatic lesions is permitted

[2] High grade dysplasia with suspicion of invasion is acceptable if approved by the MDT

- aCRC defined as either M1 or locally inoperable disease.
- Tumour RAS status either wild-type (by local testing) or unknown
- Tumour measurable by RECIST v1.1 criteria on CT scan (scans are not required to be reported to RECIST at site)
- Pre-registration laboratory tests:
  - Neutrophils ≥1.5 x10^9/l and platelet count ≥100 x10^9/l
  - Serum bilirubin ≤ 1.25 x upper limit of normal (ULN), alkaline phosphatase ≤ 5x ULN, and serum transaminase (either AST or ALT) ≤ 2.5 x ULN
  - Estimated creatinine clearance ≥50ml/min.
- Medically fit for the trial treatments
- Sufficient tumour material for EREG/AREG analysis
- Written informed consent for registration

11.4.2 Exclusion criteria for registration

- Tumour *RAS*-mutation present
- Prior chemotherapy for mCRC[4]
- Prior anti-EGFR agent therapy

Patients with previous cancers may be considered for the trial providing they meet the above eligibility criteria. It is up to clinician discretion whether a patient with dual/previous cancers is approached, dependent on stage of their other cancer and likely prognosis. Please contact the trial team at CTRU for further guidance.

11.5 Informed consent for registration

Patients will be approached for possible recruitment following MDT diagnosis and decision to treat. Suitability for inclusion into ARIEL will be assessed according to the eligibility criteria for the trial (Section 11.4). A verbal explanation of the trial and the appropriate Patient Information Sheet (PIS-1) will be provided by the attending medical staff (and/or the trial Clinical Research Nurse) for the patient to consider. Prior to registration, the patient consent will be sought for their key 'personal identifiable data' (NHS/CHI identifier, hospital/site name , date of birth, date of scan and other site specific identifiers for example patient name if mandatory at that site) to be provided to the Leeds Teaching Hospitals Trust (LTHT), to perform the central review of scans for the assessment of efficacy (section 15.10). This data will be provided by a secure and encrypted method and once received at LTHT, will be saved with only the patients trial number. This will only be applicable if the patient is randomised into ARIEL. Wherever

[4] Patients may have received neoadjuvant or adjuvant chemotherapy provided disease did not progress on treatment, and >6 months since last dose. Patients having a resection, radioembolisation or other liver-directed therapy of liver predominant disease in which there is remaining measurable extrahepatic disease may be entered into ARIEL if they otherwise fulfil all the entry criteria.

possible, this consultation will be face to face. However, if a face to face consultation is not possible, the consent discussion may be conducted remotely by telephone or video call, making sure that the patient has been correctly identified by checking the relevant identifying information as specified in the local standard operating procedures for the site. If the remote consent option is chosen, the PIS-1 and consent form must be forwarded to the patient after first making them aware of the trial, but in advance of the detailed telephone or video conversation, along with a stamped addressed envelope addressed to the local researcher for consent form return. Access may also be provided for electronic versions of PIS-1 and 2 and patients receiving PIS-1 for the first time be able to view PIS-2 if desired.

Following information provision about registration, patients will have as long as they need to consider whether they would be willing to be registered and have biological samples sent for analysis. Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. At the registration phase, the patient may be consented immediately upon provision of PIS1 and discussion. The registration phase only requires the patient's archived sample to be tested for the presence and quantity of the EREG/AREG biomarker and will not impact upon their clinical care. The patient may additionally provide consent at registration for collection of a blood sample for ctDNA analysis. ctDNA sampling is optional.

PIS1 is a prelude to the PIS2 and patient consent for randomisation. The formal assessment of eligibility may only be obtained by the Principal Investigator (PI) or an appropriate medically qualified healthcare professional. It is acceptable for the trial Research Nurse or GCP and trial trained Non-Medical Prescriber, chemotherapy nurse or research practitioner to consent the patient for registration after initial contact with the medical team.

Informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial which are out-with standard routine care at the participating site.

Site staff are responsible for:

- Checking that the correct (current approved) version of the PIS and Consent Form is used
- Checking that information on the Consent Form is complete (including patient trial number) and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the Consent Form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed, etc.)

The participant will be provided with a local contact point where he/she may obtain further information about the trial.

11.6 Registration process

Informed written consent for registration must be obtained prior to registration, subject to the patient meeting all the eligibility criteria (Section 11.4). Registration will be performed centrally using the CTRU automated 24-hour online system. To register using the web, a staff email address, a site code and Personal Identification Number (PIN) will be required. Authorisation codes and PINs will be provided by the CTRU once all the necessary documentation has been received at CTRU and the site has been fully approved.

- Participants may only be registered into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log. The following information will be required: Site code (assigned by CTRU) of the research site
- Participant details, including initials, date of birth and sex
- Confirmation of eligibility for registration
- Confirmation of date of written informed consent for registration

24-hour registration:

Web: *https://lictr.leeds.ac.uk/webrand/*

Once registration is complete, the system will allocate the participant a unique 5 digit trial number. This number together with the centre number will form the participant ID number. Confirmation of the participant registration will be emailed to the research site.

After registration, the site staff will:

- Add the unique participant ID number to the registration consent form and all CRFs
- Make sufficient copies of the signed registration consent form
- Give the patient a copy of their signed Consent Form and PIS-1. Also provide a copy of PIS-2.
- File the original (wet ink) consent form in the investigator site file and file a copy in the patient's medical notes.
- Return a copy of the completed registration consent form to CTRU (by secure file transfer – contact CTRU Data Manager for details), in line with the terms of the ethically approved consent form
- Complete the Registration Eligibility eCRF
- Record the patient details on the ARIEL Patient ID Log.

Practical notes for sample collection:

- Tumour samples need to be sent for testing as early as possible following registration to avoid delays in obtaining biomarker results. The Sample Collection and Handling process is described below.
- Tumour blocks/sections must be labelled with the trial number generated at registration and local pathology number (do not label with any personal identifiers) and sent to the designated reference laboratory.
- If the patient agrees to ctDNA sampling, the first sample will be taken in the period between registration and randomisation.
- No treatment or trial allocation will be performed at this point. The trial number will be a unique identifier and the primary way in which the patient will be identified and should be used in all correspondence throughout the registration and subsequent trial periods.

Practical notes for randomisation:

- Investigators should be cognisant of radiology requirements for randomisation – patients should have had a CT scan a maximum of 28 days prior to randomisation or 7 days after randomisation. (Patients out of these timelines would not be eligible).
- Investigators are encouraged to make arrangements for patients to start chemotherapy 2-3 weeks following registration, eg line insertion, DPYD testing

11.7 Sample Collection and Handling

All patients who consent to registration in ARIEL require prospective testing of EREG/AREG to determine their eligibility for randomisation.

In addition, RAS and BRAF testing is offered centrally, if required.

See Figure 5 for an overview of the consent and sample handling process.

Tumour samples need to be retrieved and sent to the designated central laboratory (University of Leeds and/or University of Birmingham) as soon as possible following registration to avoid delays in obtaining biomarker results and consequently treatment.

At the time of registration, consent will also be sought for the collection and storage of archival tissue for future research, and for ctDNA sampling at registration and (if randomised) on completion of the 16-week trial treatment period. Consent for future research and ctDNA sampling is optional and refusal will not preclude trial entry. If the patient has consented for their pathological material to be stored and used for future research, the tumour sample will be stored at the central laboratory in Leeds. Blood samples for ctDNA analysis will be stored in Birmingham. Note that tumour samples can be temporarily returned to site at any time during the study upon request to the CTRU, e.g. for further clinical testing.

Both laboratories are HTA-licensed with extensive experience of molecular testing in clinical trials. All material will be dealt with according to GCP, with processes overseen by a dedicated quality manager.

11.7.1 Samples to collect

Sites are asked to provide the following for all patients registered into ARIEL:

Either

- Send formalin-fixed paraffin-embedded (FFPE) tissue block(s) from the pre-treatment diagnostic biopsy or resection specimen to Leeds

Or:

- Send 10µm tissue scrolls/curls (minimum 5 scrolls) from the pre-treatment diagnostic biopsy or resection specimen (placed in Eppendorf tubes) to Birmingham. Please do not send slide mounted sections – contact the CTRU if this will present an issue

Samples must be anonymised and labelled only with the patient's ARIEL trial number (generated at registration) and pathology number. Ensure that the samples are clearly and indelibly labelled.

Bloods samples for ctDNA analysis are to be sent to Birmingham.

11.7.2. Where RAS status is unknown and not pending locally, both central RAS AND EREG/AREG testing will be required

For optimal turnaround time of results, we recommend sending scrolls to Birmingham (AREG/EREG testing) along with a completed Form 60 EREG/AREG sample submission form and block(s) to Leeds (RAS/BRAF testing) along with a Form 50 RAS/BRAF/Translational sample submission form. If you can only send block(s), send to Leeds who will cut scrolls on your behalf and forward to Birmingham. In this case, you do not need to send an F60, the Leeds lab will complete that on your behalf'

If sending scrolls and block(s) (preferable option):

For RAS/BRAF request:

The following should be carefully packaged to avoid breakage:

- anonymised, labelled FFPE block(s) (preferred) or 12 x 5µm unstained sections
- a completed **Form 50 RAS/BRAF/Translational sample** submission form
- an anonymised copy of the pathology report (with trial number included)

Send by First Class post to:

ARIEL Trial Laboratory
Pathology and Data Analytics
Level 4, Wellcome Trust Brenner building
St. James's University Hospital
Beckett Street
Leeds, LS9 7TF

For EREG/AREG request:

The following should be carefully packaged to avoid breakage:

- 10µm tissue scrolls/curls (minimum of 5 scrolls) in anonymised, labelled Eppendorf tubes
- a completed **Form 60 EREG/AREG sample** submission form

Send by First Class post to:

FAO: Elena Efstathiou
ARIEL Trial Laboratory
IBR Stores
Institute of Biomedical Research
College of Medical & Dental Sciences
University of Birmingham
Wolfson Drive
Edgbaston, Birmingham
B15 2TT

If sending only a tissue block:

The following should be carefully packaged to avoid breakage:

- anonymised, labelled FFPE block(s)
- a completed **Form 50 RAS/BRAF/Translational sample** submission form, indicating on the form that Leeds should cut scrolls and forward to Birmingham
- an anonymised copy of the pathology report (with trial number included)

Send by First Class post to:

ARIEL Trial Laboratory
Pathology and Data Analytics
Level 4, Wellcome Trust Brenner Building
St. James's University Hospital
Beckett Street
Leeds, LS9 7TF

Upon receipt, the laboratory will confirm receipt of samples with site and CTRU.

11.7.2 Where RAS status is known or pending locally, only central EREG/AREG testing is required

If sending scrolls (preferable option):

The following should be carefully packaged to avoid breakage:

- 10µm tissue scrolls/curls (minimum of 5 scrolls) in anonymised, labelled Eppendorf tubes
- a completed **Form 60 EREG/AREG sample** submission form

Send by First Class post to:

FAO:
Elena Efstathiou

ARIEL Trial Laboratory

IBR Stores
Institute of Biomedical Research
College of Medical & Dental Sciences
University of Birmingham
Wolfson Drive
Edgbaston, Birmingham
B15 2TT

Upon receipt, the laboratory will confirm receipt of samples with site and CTRU.

NB: If a patient has consented for additional translational work, then a tumour block should additionally be sent to the ARIEL pathology laboratory in Leeds, address as above, with a completed Form 50 RAS/BRAF/Translational sample submission form.

If sending block(s):

The following should be carefully packaged to avoid breakage:

- anonymised, labelled FFPE block(s)
- a completed **Form 50** RAS/BRAF/**Translational sample** submission form, indicating on the form if Leeds should cut scrolls and forward to Birmingham for EREG/AREG testing (You will not need to include an F60 as the Leeds lab will do that for you)
- an anonymised copy of the pathology report (with trial number included)

Send by First Class post to:

ARIEL Trial Laboratory
Pathology and Data Analytics
Level 4, Wellcome Trust Brenner building
St. James's University Hospital
Beckett Street
Leeds, LS9 7TF

Upon receipt, the laboratory will confirm receipt of samples with site and CTRU.

11.7.3 Biomarker test results

The central laboratories will perform RAS/BRAF and/or ERAG/AREG testing.

EREG/AREG will be measured by reverse transcriptase polymerase chain reaction (RT-PCR) and dichotomised (either high vs both low) using predefined cut-points.

Results of the central laboratory testing for RAS status and EREG/AREG status will be fed back to sites via the ARIEL Database – section "ARIEL Lab Database". The CTRU will endeavour to send a reminder email to the site team to check the ARIEL Lab Database for the lab result. Sites are responsible for confirming whether the patient is eligible to be considered for randomisation via the ARIEL Database.

Central results will only be available to view on the lab database section for the ARIEL study.

The anticipated turnaround for biomarker status is 7-10 days.

11.7.4 ctDNA sample collection (optional)

Sites will be provided with PAXgene Blood ccfDNA Tubes (or suitable alternative tubes). Two 10ml tubes should be collected on a single occasion in the period between registration and randomisation for all patients who provide consent (NB a second sample will also be taken at the 16-week follow-up visit for those who undergo randomisation). Sampling should be timed to coincide with routine trial blood tests or standard of care blood tests in order to avoid additional visits or venepuncture.

Please note, blood samples from patients with HIV or viral hepatitis infection risk are not accepted by the trial laboratory. Such patients should note be asked to provide samples for ctDNA.

Samples should be labelled with the participant's trial number, and the date and time the sample was taken. An ARIEL ctDNA sample collection form should also be completed, detailing the date and time of sample collection, trial number, timepoint of sampling within the trial (i.e. sample taken at registration, or sample taken on completion of 16-week trial treatment period), site, and name of person performing sample collection. A copy should be made of the sample collection form to keep in the ISF and the original enclosed with the samples.

Samples must be kept at room temperature and, as soon as possible, sent in the packaging provided to:

ARIEL Trial Laboratory ctDNA sample collectionBeggs Group,IBR Stores
Institute of Biomedical Research
College of Medical & Dental Sciences
University of Birmingham
Wolfson Drive
Edgbaston, Birmingham
B15 2TT

11.8 Chemotherapy during registration stage

Ideally chemotherapy should commence when ARIEL biomarker results are available, and eligible patients are randomised. It is anticipated that biomarker testing should take 7-10 days and within an acceptable window whilst other pre-chemotherapy procedures are ongoing (e.g. PICC line insertion; DPYD testing). However some investigators may elect to commence chemotherapy whilst awaiting biomarker results, particularly if a patient is very symptomatic.

One cycle of chemotherapy is permitted during the registration stage. r[5]Treatment of patients with RAS mutation or EREG/AREG low levels

If biomarker results confirm that a patient either has a RAS mutation or EREG/AREG low levels, then they cannot be randomised in the ARIEL trial and they are considered 'off-trial'. They should proceed to off-trial treatment as directed by their oncologist.

We have chosen not to randomise patients with EREG/AREG low levels as there is consistent evidence showing a lack of benefit with anti-EGFR agents in this population. However to better understand the implication of this biomarker result we will plan to conduct future translational research on collected samples and conduct a single data collection at 1 year. This will help us better understand this biomarker group compared with the EREG/AREG high population and explore treatment targets for this underserved population.

Data collection at 1 year will include:

- Summary of treatment
- Progression events
- Locally assessed radiological response to 1st line chemotherapy
- Survival events

Patients do not require a specific trial visit for this assessment; data will be available from digital records.

[5] If a regimen that includes capecitabine is chosen, this will need to be changed to a different regimen if the patient is randomised to the chemotherapy with anti-EGFR arm.

12 Randomisation Stage

The ARIEL trial aims to randomise 162 patients over a 3 year period.

12.1 Eligibility for randomisation

Patients meeting all of the inclusion criteria, and none of the exclusion criteria, will be considered for participation in the trial. Eligibility waivers to any of the inclusion and exclusion criteria are not permitted. Informed consent must be obtained prior to undertaking any trial-specific procedures, including non-routine screening investigations and assessments.

12.1.1 Inclusion criteria for randomisation

- Registered in ARIEL
- ARIEL central or local testing confirms tumour RAS-wt status (see section 11.3) for local testing criteria)
- ARIEL central testing confirms tumour EREG/AREG high
- Patients have had CT scan within the timeframes stipulated in section 15.2 (If there is a contrast reaction, then non-contrast CT with MRI is acceptable assuming at least one of these modalities shows measurable disease at baseline for ETS evaluation and both modalities are repeated at the 2 trial timepoints at week 8 and 16.)
- WHO performance status (PS) 0, 1 or 2 (see Appendix A)
- For women of childbearing potential, negative pregnancy test as per standard practice and adequate contraceptive precautions (section 12.4).F
- Effective contraception for male patients if the risk of conception exists (section 12.4).
- Fit for combination chemotherapy plus cetuximab/panitumumab
- Written informed consent for randomisation.

12.1.2 Exclusion criteria

- Patient has received more than one cycle of chemotherapy since registration
- Women who are breastfeeding
- Patients with history of hypersensitivity to irinotecan, oxaliplatin, 5-fluorouracil or any of their excipients
- Patients in receipt of live vaccine within four weeks prior to randomisation.
- Patients with a history interstitial pneumonitis/idiopathic lung disease (ILD)
- Patients with a history of keratitis, ulcerative keratitis or severe dry eye
- Patients with a history of severe skin reaction which in the clinicians opinion could be exacerbated by EGFR Mab (cf Steven's Johnson Syndrome)

12.2 Post-registration treatment in patients with low EREG/AREG

Patients with low tumour EREG/AREG will not be eligible for randomisation and will be treated, according to physician discretion. Information regarding clinical outcomes with anti-EGFR treatment in this biomarker group is available in the introduction (section 5.2.3).

Basic information will be collected about treatment given and clinical outcomes using a single CRF completed 1 year after registration.

12.3 Informed consent for randomisation

PIS-2 must be provided to the patient prior to randomisation, this may be once the biomarker panel results are complete and the Leeds CTRU has informed the site that the patient is eligible for randomisation or at an earlier stage including at the time of PIS-1 and registration as the patient requires. A verbal explanation of the trial and PIS-2 will be provided by the attending medical staff (and/or the trial Clinical Research Nurse) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the trial. Wherever possible, this consultation will be face-to-face. However, if a face-to-face consultation is not possible, the consent discussion may be conducted remotely by telephone or video call, making sure that the patient has been correctly identified by checking the relevant identifying information as specified in the local standard operating procedures for the site. If the remote consent option is chosen, the PIS-2 and consent form must be forwarded to the patient in advance of the telephone or video call, along with a stamped addressed envelope addressed to the local researcher.

Following information provision, patients will have as long as they need to consider participation, normally a minimum of 24 hours, and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The formal assessment of eligibility and informed consent may only be obtained by the Principal Investigator (PI) or an appropriate medically qualified healthcare professional.

Informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial which are out-with standard routine care at the participating site.

Site staff are responsible for:

- Checking that the correct (current approved) version of the PIS and Consent Form is used
- Checking that information on the Consent Form is complete (including patient trial number) and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the Consent Form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed, etc.)

Following randomisation:

- Making sufficient copies and filing the original consent form in the investigator site file, and filing a copy in the patient's medical notes.
- Giving the patient a copy of their signed Consent Form, PIS and patient contact card.
- Sending a copy of the signed consent form to CTRU vial the Secure File Transfer system in line with the terms of the ethically approved consent form.

The participant will be provided with a local contact point where he/she may obtain further information about the trial.

12.4 Birth control, pregnancy testing and conservation of sperm

Female patients of childbearing potential should be advised to avoid becoming pregnant while receiving treatment and for 6 months after the last dose. Female patients of childbearing potential OR male patients who are sexually active with a woman of childbearing potential should be advised to use a highly effective method of contraception while receiving treatment and until 6 months after finishing treatment. Pregnancy testing should be undertaken pre randomisation, monthly during trial treatment and one month after the last dose of trial treatment.

Investigators should advise male patients to seek advice on conservation of sperm prior to treatment, due to potential anti-fertility effect of chemotherapy which could be irreversible.

12.5 Prior and concurrent participation in other clinical trials

Participation in therapeutic clinical trials is not permitted up to the 8 week primary endpoint assessment. However, participation in non-therapeutic registry studies or questionnaire-based studies is permitted. Questions about potential clinical trials can be addressed to the Chief Investigators via CTRU prior to randomisation.

12.6 Randomisation process

Informed written consent for randomisation must be obtained prior to randomisation.

Randomisation will be performed centrally using the CTRU automated online system. To randomise using the web, a staff email address, a site code and Personal Identification Number (PIN) will be required. Authorisation codes and PINs will be provided by the CTRU once all the necessary documentation has been received at CTRU and the site has been fully approved.

Participants may only be randomised into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log.

The following information will be required:

- Site code (assigned by CTRU) of the research site

- Participant details, including initials and date of birth (which must match details provided at registration)
- Participant's unique trial number provided at registration
- Confirmation of eligibility for randomisation
- Confirmation of date of written informed consent for randomisation
- Confirmation of completion of baseline quality of life and health economics questionnaires
- Confirmation of minimisation factors (see below).

24-hour randomisation:

Web: *https://lictr.leeds.ac.uk/webrand/*

Please ensure that you have completed the Randomisation Form and that patients have completed the baseline questionnaires before accessing the web randomisation

12.7 Treatment allocation

Patients eligible for the randomised element will be allocated 1:1 to chemotherapy alone or chemotherapy plus anti-EGFR agent, using minimisation with a random element. The trial is open-label, therefore participants, trial site research teams and the CTRU trial team will be aware of the allocation.

A computer-generated minimisation programme that incorporates and random element will be used to ensure that treatment groups are well balanced for the minimisation factors which will include:

- Choice of first-line chemotherapy (irinotecan vs oxaliplatin-based vs other[6])
- Tumour location (transverse vs caecum vs ascending)
- Prior adjuvant or neoadjuvant chemotherapy (yes vs no)
- Primary tumour resected (yes vs no)

Once randomisation is complete, the system will allocate the treatment allocation (chemotherapy alone or chemotherapy plus anti-EGFR agent) for that participant.

12.8 Loss of capacity following informed consent

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

[6] For patients who receive chemotherapy with both irinotecan and oxaliplatin (e.g.Single Agent Fluorouracil), the 'other' option should be selected

Participants who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the PI and participant's carer/family, with the participant's best interests foremost in the decision making process. Ongoing collection of safety and follow-up data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention to treat analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

12.9 Non-registration screening data

In order to determine the generalisability of the trial results, and for Consolidated Standards of Reporting Trials (CONSORT) requirements, participating research sites will be required to complete a Non-Registration log for all those patients who are not registered into the trial. Anonymised data will be collected including:

- Age
- Gender
- Ethnicity
- Date screened
- Reason for non-registration:
    - The reason that a patient was not approached, or
    - The reason that a patient declined registration

However, the right of the patient to refuse consent for registration without giving reasons will be respected. This information will be requested from participating sites on a regular basis (at least 3 monthly) by the CTRU.

13 Trial Medicinal Product Management

13.1 IMP definition

Within the ARIEL trial, only the anti-EGFR agents, cetuximab and panitumumab, are classed as Investigational Medicinal Products (IMPs).

13.2 Cetuximab and Panitumumab composition

- Cetuximab is a chimeric monoclonal IgG1 antibody. It is commercially available as a 5mg/ml solution for infusion.

- Panitumumab is a fully human monoclonal IgG2 antibody. It is commercially available as a 20mg/ml concentrate for solution for infusion.

For further details of the composition of either IMP, refer to the current version of the manufacturer's Summary of Product Characteristics (SPC), which can be accessed via the electronic medicines compendium (emc) website https://www.medicines.org.uk/emc/.

13.3 IMP supply and handling

Both cetuximab and panitumumab are licensed in the UK and in general commercially available 'off the shelf' pharmacy supplies will be used. IMP will not be provided by the ARIEL trial. There is no requirement to ring-fence cetuximab or panitumumab for the ARIEL trial. Both IMPs will be handled in line with the manufacturers' recommendations, as per the current version of the relevant SPC.

13.3.1 Use of 3rd party supply and delivery of IMP

IMP supply and delivery to a participant's home by 3rd party home healthcare companies is permitted if this is in accordance with routine NHS practice at the participating trial site. The trial does not require any additional actions beyond existing standard care practices. CTRU should be informed during the site set-up process, or if this is adopted during the life of the study. This arrangement must be documented in the model Non-Commercial Agreement between the Sponsor and participating site.

13.4 IMP formulation, storage and preparation

Cetuximab and panitumumab formulation, storage and preparation is in line with the manufacturers' recommendations, as per the current version of the relevant SPC (via https://www.medicines.org.uk/emc/).

13.5 IMP prescribing and labelling

Cetuximab and panitumumab will be used in accordance with the conditions set out in Regulation 46 (2) of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and

amended in 2006). As both IMPs will be used within their licensed indication, no special trial prescribing or labelling requirements apply. Both IMPs may be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisation etc.) Regulations 1994

13.6 IMP accountability

As general 'off the shelf' pharmacy supplies will be used, no trial-specific accountability logs are required. Dispensing records will be in line with local standard practice and as a minimum will ensure that IMP is fully traceable by batch number.

The trial pharmacist will sign a document to confirm that local hospital systems are in place to cover drug ordering, drug receipt, drug storage and dispensing, and will enable accurate traceability of all drugs used in the trial.

Unused, used or partially used stocks of IMP should be disposed of at site according to local policy.

13.7 Non-IMPs

The following drugs are classed as non-IMPs in this trial:

- 5FU
- folinic acid
- oxaliplatin
- capecitabine
- irinotecan
- raltitrexed
- bevacizumab

14 Treatment Details

The ARIEL trial is a purposely pragmatic trial, aimed to assess the use of EREG/AREG to identify right-PTL patients who will benefit from anti-EGFR agents as part of standard care, compared with chemotherapy alone.

For patients randomised in ARIEL, they will receive a 16-week duration of chemotherapy +/- anti-EGFR agent. Therefore, ARIEL trial treatment is in line with NICE recommendation for RAS-wt aCRC (Technology Appraisal TA439 and NICE Guideline NG151) [25, 26] .Standard doses, schedules and adaptations for toxicity can be used (see Appendix B).

Treatment should start as soon as possible after randomisation. Patients should be reviewed prior to each cycle of treatment to assess for toxicity and any evidence of disease progression (nurse-led and virtual pre-assessment is acceptable as per local practice).

It is preferable that treatment begins following randomisation but if a delay due to biomarker testing is unacceptable then 1 cycle of chemotherapy is permitted prior to randomisation. If 1 cycle of chemotherapy is given prior to randomisation (this is given off trial), ensure that all pre-randomisation assessments are still within the required timeframes (see section 15.2).

14.1 Randomisation to treatment with chemotherapy plus anti-EGFR agent

Sites are encouraged to utilise local protocols that are within this guidance; guidance is available in Appendix B. The anti-EGFR treatment is a choice (not randomisation) between **either cetuximab or panitumumab.** The chemotherapy backbone is also ‘dealer’s choice’.

Clinicians must decide ahead of randomisation which regimen will be used to ensure that the randomisation is balanced for these factors.

As per NICE TA439, both cetuximab and panitumumab are given in combination with either:

- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

Therefore treatment with a chemotherapy backbone including capecitabine is not recommended.

Treatment should commence as soon as possible following randomisation, but if a delay due to biomarker testing is unacceptable, then 1 cycle of chemotherapy is permitted prior to randomisation.

This treatment should be delivered on a 14 day schedule, with safety assessments up to 72 hours beforehand.

14.2 Randomisation to treatment with chemotherapy alone

Patients randomised to chemotherapy alone should be treated as per local guidelines with any of the permitted regimens as listed below. Choice of regimen will depend upon individual patient characteristics and choices, as judged by their oncologist. If the oncologist wishes to use a different regimen than those listed then they should contact the study team.

Standard chemotherapy regimens that are acceptable during first-line treatment include the following:

- FOLFOX (OxMdG) (5FU, folinic acid and oxaliplatin)
- XELOX (oxaliplatin and capecitabine)
- FOLFIRI (IrMdG) (5FU, folinic acid and irinotecan)
- Irinotecan and capecitabine
- Oxaliplatin and raltitrexed

Bevacizumab may also be administered in combination with the standard chemotherapy regimen. At the point of this protocol bevacizumab is not reimbursed by NICE; if an investigator wishes to use bevacizumab in this arm, then they should contact the ARIEL team.

FOLFOXIRI is not allowed within the trial.

Treatment should commence as soon as possible following randomisation, but if a delay due to biomarker testing is unacceptable, then 1 cycle of chemotherapy is permitted prior to randomisation.

Safety assessments to be performed up to-72 hours prior to each cycle.

14.3 Initial dosing and dose reductions

Patients should ideally receive full doses of all drugs as per surface area, however an initial dose reduction to 80% of any, or all, drugs is permitted.

Dose reductions – should be as per local guidance but guidance is provided in Appendix B.

Dose delays are permitted as per local guidelines for resolution of toxicity. However please note that the radiological assessment periods should correspond as closely with 8 and 16 weeks of treatment as possible.

Dose capping is acceptable as per local guidance.

14.3.1 DPYD Testing

We recommend that patients should have a DPYD germline mutation assessment to inform dosing of 5FU. Standard dosing should be used in patients with no identified reduced function variants. Patients heterozygous for a reduced functional variant should be dosed based on the advice of the DPYD report, or as per local policy. Patients homozygous for DPYD germline mutation should be withdrawn from the study.

14.4 Management of toxicity

All trial treatments within ARIEL are standard treatments, toxicity management should be as per local guidance. Standard toxicity guidelines specific to anti-EGFR agents are detailed in Appendix B.

14.5 Treatment Duration

The study period is the first 16 weeks of 1st line chemotherapy. Following this period, treatment is as per investigator and patient preference (for example, continuation of chemotherapy +/- anti-EGFR, maintenance treatment or treatment break).

The planned duration of this protocol treatment should be as near 16 weeks of treatment as possible with a window of ±2 weeks (14-18 weeks permissible). Hence the study treatments described in Sections 14.1 and 14.2 should be prescribed for a 14 week period as a minimum.

Please note that stopping trial treatment does not constitute withdrawal from the research.

14.6 Cessation of treatment

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. All participants who discontinue treatment or are prescribed alternative treatment will still attend for follow-up assessments unless unwilling to do so and CRFs will continue to be completed.

Reasons for discontinuation of treatment include:

- disease progression
- unacceptable toxicity, in the opinion of the investigator or participant (Appendix B)
- participant decision (withdrawal of consent) (Section 15.9)
- pregnancy (Section 15.12)
- comorbidity preventing continuation.

14.7 Supportive care

Supportive medications should be prescribed as per local guidance and should be used as required.

14.8 Further post protocol defined anti-cancer treatment

No specific recommendations are made regarding further post protocol defined anti-cancer treatment. Treatment should be as per local policy.

14.9 Prohibited Concomitant Medications

Trial participants are prohibited from the following:

- Live vaccines during the study and for three months after the last dose of IMP
- CYP3A4/5 inhibitors and inducers (in patients receiving irinotecan)

14.10 Phototoxicity

Investigators must advise participants to engage in UV-light minimisation measures such as applying high SPF sunscreen and wearing hats, pants, and long sleeves during participation in the study and for the duration of five-half lives of panitumumab stated as 40 days.

15 Trial Assessments and Data Collection

Participating sites will record trial participant data on electronic Case Report Forms (eCRFs) in a trial-specific database. Missing and discrepant data will be flagged and additional data validations raised as appropriate from the CTRU data management team.

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Participant-completed Quality of Life and health economics questionnaires will be completed on paper CRFs. The questionnaires can be completed either in the clinic or, if a clinic visit is not possible, posted to the participant for completion at home. If they are completed by the participant in clinic, they should be sealed in an envelope before handing back to the site research team who will return them to the CTRU via post. If they have been posted to the participant for completion at home, an addressed envelope should be provided so that the questionnaires can be posted directly back to the team at the CTRU. Questionnaires completed by the participant must not be copied or retained by the site.

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File, ISF), which will be provided by the CTRU, and keep copies of all completed Case Report Forms (CRFs) for the trial. The CRFs and participant-completed Quality of Life questionnaires will contain the participant's unique trial number, date of birth, and initials.

CRFs/eCRFs must only be completed by personnel authorised to do so by the Principal Investigator, as recorded on the trial-specific Authorised Personnel Log.

The timing of assessments are summarised in the following tables and paragraphs:*

Table 15-1- Assessment schedule

	Pre-registration	Pre-randomisation	Monthly whilst receiving treatment	Prior to first cycle of trial treatment	Prior to each cycle of treatment	Week 8 (post treatment start)	Week 16 (post-treatment start)	Annual follow-up[7]
Histological confirmation of colorectal cancer	X							
Imaging confirming metastatic cancer	X							
Clinical evaluation (including vital signs)[8]		X			X	X	X	
Consent	X PIS-1	X PIS-2						
CT scan[9]		X[10]				X[11]	X[12]	
Tumour sent for central testing		X[13]						
Confirmation of RAS status		X						
Confirmation of EREG/AREG status		X						
FBC, U&Es[14], LFTs[15]	X				X[16]			
CEA	X					X[17]	X[18]	
ctDNA sampling		X					X	

[7] All patients will be followed up to one-year post-randomisation as a minimum with a final assessment in all patients when the last patient has completed a year of follow-up.

[8] Vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature

[9] If there is a contrast reaction, then non-contrast CT with MRI is acceptable assuming at least one of these modalities shows measurable disease at baseline for ETS evaluation and both modalities are repeated at the 2 trial timepoints at week 8 and 16.

[10] To be performed a maximum of 28 days prior to randomisation OR scheduled to occur a maximum of 7 days after randomisation

[11] At 8 weeks (+/- 1 week)

[12] At 16 weeks (+/- 1 week)

[13] Tumour samples need to be retrieved and sent to the designated central laboratory (University of Leeds and/or University of Birmingham) as soon as possible following registration to avoid delays in obtaining biomarker results and consequently treatment.

[14] U&Es include sodium and potassium

[15] LFTs include ALT or AST, ALP and serum bilirubin

[16] Within 72 hours prior to starting each cycle. For the 1st cycle of chemotherapy, within 10 days prior to starting treatment.

[17] CEA is to be performed as per local standard of care – most recent available CEA results will be collected at the 8-week FU timepoint

[18] CEA is to be performed as per local standard of care – most recent available CEA results will be collected at the 16-week FU timepoint

	Pre-registration	Pre-randomisation	Monthly whilst receiving treatment	Prior to first cycle of trial treatment	Prior to each cycle of treatment	Week 8 (post treatment start)	Week 16 (post-treatment start)	Annual follow-up[7]
DPYD mutation testing				X[19]				
Magnesium monitoring		X			X[20]			
WHO Performance Status		X[21]						
Negative pregnancy test		X[22]	X				X[23]	
Confirmation of eligibility	X	X						
Toxicity assessment					X	X	X	
QoL and health economics questionnaires		X				X	X	X[24]
eCRF data collection		X			X	X	X	X

[19] We recommend (but do not mandate) that patients should have a DPYD germline mutation assessment to inform dosing of 5FU before the first cycle of trial treatment.

[20]. Magnesium monitoring is recommended for patients receiving cetuximab and panitumumab

[21] Within 1 week prior to randomisation

[22] This must be a highly sensitive serum pregnancy test

[23] A final pregnancy test is required one month after last dose of trial treatment

[24] At 12 months post-randomisation,and may be by post.

15.1 Pre-registration eligibility assessments

The following investigations must be performed to establish eligibility for registration:

- Diagnostic biopsy
- Imaging confirming metastatic cancer
- FBC, U&Es, LFTs and CEA (must be done in line with local protocols prior to registration to confirm fitness to receive protocol treatment)

15.2 Pre-randomisation and baseline eligibility assessments

The following investigations and assessments **must be carried out prior to randomisation**. **Written informed consent must be obtained before any assessments that are not part of standard care**.

- Confirmation of EREG/AREG high status
- Confirmation of RAS-wt status
- Clinical evaluation (clinician or nurse led) including vital signs
- CT scan of chest, abdomen and pelvis with RECIST v1.1 evaluable disease
    - A maximum 28 days prior to randomisation
    - OR scheduled to occur a maximum of 7 days after randomisation.
- WHO Performance status (within 1 week prior to randomisation)
- Negative pregnancy test as per standard practice (if the participant is a woman of childbearing potential) This must be a highly sensitive serum pregnancy test.
- Completion of the baseline QoLand health economics questionnaire by the participant (to be completed after consent for randomisation but before randomisation)
- ctDNA sampling (where optional consent was obtained – see section 11.7.4)

15.3 PICC line insertion

Where the chosen chemotherapy and/or randomisation allocation requires it, a PICC line should be inserted prior to treatment, in line with standard local procedures, including X-ray to check positioning. The timing of this is at the discretion of the local investigator and may take place whilst the results of the biomarker testing are awaited (anticipated to take 7-10 days). Ideally chemotherapy should commence when ARIEL biomarker results are available, and eligible patients have been randomised, but if a delay due to biomarker testing is unacceptable then 1 cycle of chemotherapy is permitted prior to randomisation.

15.4 Pre-treatment assessments

Treatment should start as soon as possible after randomisation. The following assessments should be undertaken

- Clinical evaluation (clinician or nurse led) including vital signs
- FBC, U&Es, LFTs (within 10 days prior to treatment start)
- DPYD mutation testing is encouraged but not mandated
- Magnesium monitoring is recommended with cetuximab and panitumumab

Investigations / assessments carried out at pre-registration do not need to be repeated if done within 10 days prior to trial treatment starting.

15.5 Assessments during treatment

Participants allocated to both arms of treatment should be assessed for safety in accordance with standard clinical practice at site. It is expected that the following assessments should be undertaken prior to each cycle of treatment:

- Clinical evaluation (clinician or nurse led) including vital signs
- Toxicity assessment
- Blood tests (FBC, U&E, LFTs) should be performed within 72 hours prior to starting each cycle (except for the 1st cycle of treatment, where assessments should be within 10 days prior to treatment start)
- Magnesium monitoring is recommended with cetuximab and panitumumab
- Monthly pregnancy tests for women of child bearing potential (WOCBP)

Any other pre-treatment assessments performed as standard practice at trial sites should continue to be performed.

15.6 Follow-up assessments post-randomisation (both arms)

Follow-up will take place at **8 and 16 weeks post-start of trial treatment** (+/- 1 week) for both arms of patients. If a patient receives cycle 1 prior to randomisation, this does not count as trial treatment and the follow up assessments are counted from the start of trial treatment post randomisation. It is acceptable for the follow-up CT scans to occur ± 1 week from the 8 or 16 week time point.

The following assessments will be undertaken at each follow-up visit:

- Clinical evaluation including vital signs
- Toxicity assessment
- CT scan of chest, abdomen and pelvis (with local radiology assessment)
- CEA - to be performed as per local standard of care – most recent available CEA results will be collected at the follow-up timepoints
- QoL and health economics questionnaire
- Overall treatment utility

A blood sample for ctDNA analysis (two 10ml PAXgene Blood ccfDNA Tubes or suitable alternative tubes) will be taken at the 16 week follow-up visit where the optional consent for this has been given (see section 11.7.4 for information regarding packaging and dispatch).

A final pregnancy test is required one month after the last dose of trial treatment, for women of child bearing potential (WOCBP).

15.7 Follow up Assessments After End of Trial Treatment

Following 16 weeks, radiological assessment will be at the discretion of the treating clinician, however, it is normal UK practice for patients with responding or stable disease to have a treatment break or reduced dose maintenance chemotherapy at this point.

Sites will complete a follow-up CRF at 12 months post-randomisation. A final follow-up CRF will also be completed for all patients when the last patient has completed a year of follow up. The follow-up CRF will collect information on:

- Progression status
- Anti-cancer treatment administered after end of trial treatment
- Overall survival
- QoL and health economics questionnaire at 12 months post-randomisation

At the 12 months post-randomisation time point, unless the participant is being seen in clinic, the research team at site will post the questionnaire pack to the participant's home address, along with a stamped-addressed envelope (addressed to CTRU), for the patient to complete and post back.

15.7 Duration of follow-up

All patients will be followed up to one-year post-randomisation as a minimum with a final assessment in all patients when the last patient has completed a year of follow up – median 3.5 years follow up.

15.8 Protocol deviations

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

15.9 Withdrawal of consent

Patients will be informed about their right to withdraw from the study and that this will not affect their subsequent care. The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal eCRF, in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

Follow-up data will continue to be collected, including data collection through linkage to NHS data systems, unless the patient explicitly states they do not wish to contribute further data to the study.

It should be made clear to any participant specifically withdrawing consent for <u>further data collection</u> that further data pertaining to <u>safety</u> will continue to be collected, for example the outcome of an event that was reported prior to withdrawal, and will be included in any safety analysis. In addition it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future. It is not possible to withdraw data which has already been collected.

15.10 Assessment of efficacy – central review of Trial Radiology StudiesC

All patients that undergo randomisation will be followed up to assess early tumour shrinkage (ETS). Contrast enhanced CT scans are the preferred method. MRI is reserved for patients where CT contrast cannot be administered with prior agreement with the Clinical Trials team – in this case a non contrast CT of the chest abdomen and pelvis should be performed with MRI assessment at each assessment. At least one of the modalities should demonstrate measurable disease for ETS assessment at the baseline and both modalities repeated at later trial endpoints. ETS is measured as the sum of maximum diameters (SMD) of RECIST target lesions on the baseline CT scan vs the SMD of the same lesions, measured in the same orientation, after 8 weeks of treatment. ETS achievement will be taken as a binary yes/no variable and is defined as a reduction of at least 30% in SMD.

All relevant imaging should be made available for central review.

Key personal identifying data and the date of the CT scan/MRI scan will be required to identify and access the scans via the NHS imaging portal.

15.11 Deaths

All deaths occurring from the date of randomisation to the end of follow-up must be recorded on the Notification of Death CRF and sent to the CTRU within 5 days of the site team becoming aware of the death.

15.12 Pregnancies

All pregnancies and suspected pregnancies in a trial participant, or their partner, occurring from the date of randomisation until six months after completion of protocol treatment must be reported to the CTRU within 24 hours of the site becoming aware. All protocol treatment must be stopped immediately if a pregnancy in a female participant occurs or is suspected.

The CTRU will report all pregnancies occurring during and within six months after completion of protocol treatment to the Sponsor along with any follow-up information. CTRU will follow up the pregnancy of any trial participant or partner of a male participant, to outcome and any congenital abnormality or birth defect resulting from the pregnancy should be reported as a Serious Adverse Event.

15.13 Participant transfer to another site

If a participant is transferred to a different site, the Participant Transfer eCRF needs to be completed. Copies of any paper CRFs, Informed Consent documents and any other relevant correspondence is sent to the new site, with originals kept at the original site. Data from before the date of transfer will be queried with the original site and data from after the date of transfer will be queried with the new site.

15.14 End of trial definition

The end of the trial is defined as the date of the collection of the last participant data item.

16 Quality of Life

16.1 Background

A number of recent trials have reported on the impact on global QOL of cetuximab or panitumumab in combination with two cytotoxic agents (FOLFIRI or FOLFOX4) in a first line aCRC setting; with skin toxicity grade or early tumour shrinkage not found to impact on global QOL scores.[27-29] However, one of the limitations in these combination trials is the lack of inclusion of a disease specific questionnaire (e.g. EORTC QLQ-CR29), and consideration of addition items to cover toxicities specific to anti-EGFR agents (e.g. skin toxicity). In this study we will address both of these issues to more fully describe patient experience using patient-reported outcomes (PROs).

16.2 Methods

PROs for assessment of HRQOL, symptomatic toxicity and health economic analysis will be assessed at randomisation (prior to knowledge of trial arm), 8 weeks, 16 weeks and at 12 months in line with clinical and imaging assessments with flexibility given for exact timings of form submission. PROs will be completed on paper at the time of clinic appointments using the (English-version) EORTC QLQ-C30, EORTC QLQ-CR29 disease specific module with additional items to cover anti-EGFR symptomatic toxicity using the EORTC-QLQ item library, and the EQ5D.[30-33]

EORTC-QLQ and EQ5D guidelines for analyses and management of missing data will be followed and reported according to CONSORT-PRO[34, 35]. Mean scores and 95% CIs for all items at each time-point will be reported and exploratory analyses of symptoms predictive of tumour response and impact on global QOL will be evaluated.[36]

17 Health Economics

We will conduct an economic evaluation of the EREG/AREG stratification and treatment strategy vs standard care. We will follow the NICE appraisal reference case[37] and as such present incremental costs per quality-adjusted life year (QALY) from the perspective of the health and social care provider. We will report outcomes over 12 month and lifetime horizons. Participants will complete the EQ-5D-3L at baseline and all follow-up points; this data, along with survival, will be used to estimate QALYs. Supplementary analyses will base QALY estimation on utility indexes derived from the EORTC QLQ-C30 measure (EORTC-8D[38] and QLU-C10D[39]). Patients will also report primary care resource use in a bespoke questionnaire. Secondary healthcare use will principally be captured via an NHS Digital request at the end of study. Medicines use will be captured in the trial CRFs and we will record any diagnostic test and interpretation costs. These resource elements will be costed using existing unit cost databases (e.g. BNF, eMIT, PSSRU Report and NHS Reference Costs).

Seemingly unrelated regression models will be used to analyse cost and QALY data during the trial follow-up, to account for correlation between the two outcomes. Where appropriate, this will mirror the statistical team approach to incorporating control variables and adjust for the specified minimisation factors. Adjustments will also be made for any imbalance in baseline costs and utility, if necessary. Parametric or non-parametric (i.e. bootstrapping) methods will be used to characterise the sampling uncertainty present with simulations plotted on a cost-effectiveness plane and cost-effectiveness acceptability curves.

Multiple imputation will be used to impute missing data. The type and degree of missing data will be assessed and evaluated as to whether the assumption of missing at random (MAR) holds.[40] Should MAR not hold we will explore the impact of alternative assumptions.[41]

A long-term decision model will extrapolate the costs/benefits of the treatment strategies over a lifetime horizon. The model will be developed following best practice [42] with PPI and clinician input. The parameter values will be derived from trial data, targeted literature reviews and, if feasible, from the CORECT-R colorectal cancer data repository. One year cumulative cost and QALY data (and related variance) generated from the trial will feed into the model at initiation.

The model will enable the assessment of parameter uncertainty in deterministic and stochastic sensitivity analyses and allow characterisation of uncertainty around diagnostic accuracy. Monte Carlo simulations using draws from parameter distributions will allow a probabilistic sensitivity analysis capturing total parameter uncertainty in the model. Results will be reported in terms of incremental cost-effectiveness ratios, net benefit distributions and cost-effectiveness acceptability curves.[43] A cost-effectiveness threshold of £20,000 per QALY gained will be assumed.

Costs and benefits post 12 months will be discounted at a rate of 3.5% per annum as per NICE guidance. NICE is currently updating the guidance for technology appraisals and a review of the planned methods stated here will be undertaken, considering the updated guidance when published. A detailed health economic analysis plan (HEAP) will be generated.

Data requirements:

For Health Economics

Measure/Data	**Time-points**	**Pages**
EQ-5D 3L	Baseline and all follow-up	2
Primary and social care resource use	Baseline and all follow-up	2

Other data we will require access to

Measure/Data
EORTC QLQ-C30
EORTC QLQ-CR29
Survival status and date of death
Medicine use
Diagnostic tests
CRF data on hospital stays/LoS if available
HES – Secondary care data
CORECT-R – exact data to be determined

18 Translational Science

Details of tumour tissue collection is listed in Section 11.7. This occurs at the point of registration. Consent is requested for both trial specific molecular analysis (RAS/BRAF and/or EREG/AREG) and for the collection and storage of archival tissue and residual RNA, extracted for RAS/BRAF/EREG/AREG analysis, for future research. Consent for future research is optional and refusal will not preclude trial entry.

If the patient has consented for their pathological material to be stored and used for future research, a tumour block should be sent to (even if RAS/BFRAF testing is not required):

ARIEL Trial Laboratory
Pathology and Data Analytics
Level 4, Wellcome Trust Brenner Building
St. James's University Hospital
Beckett Street
Leeds
LS9 7TF

Enclose a completed Form 50 RAS/BRAF/Translational sample submission form.

The tumour block and residual RNA will be stored at the central laboratory (University of Leeds and University of Birmingham, respectively), until such a time that they are released to other laboratories for use in ethically-approved research.

Details of the RAS/BRAF and EREG/AREG analysis and laboratory QA are detailed in the Laboratory SOPs held by the central laboratories.

19 Toxicity Reporting

19.1 General definitions

19.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with the IMP treatment.

19.1.2 Adverse Reaction (AR)

Adverse reactions (ARs) are all untoward and unintended responses to the IMP trial treatment (anti-EGFR agents). This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

19.1.3 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that:

- results in death.
- is life-threatening.
- requires inpatient hospitalisation or prolongation of existing hospitalisation.
- results in persistent or significant disability or incapacity.
- consists of a congenital anomaly or birth defect.
- is otherwise considered medically significant by the Investigator.

19.1.4 Serious Adverse Reaction (SAR)

A Serious Adverse Reaction (SAR) is an SAE deemed to have been related to the IMP trial treatment (anti-EGFR agents). Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol Section 19.4 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

19.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product as set out in the Reference Safety Information (RSI) within the current trial-approved version of the applicable SPC (Section 19.1.6). Severity describes the intensity of the event. Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol section 19.4 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

19.1.6 Reference safety information

The Reference Safety Information (RSI) in this trial is defined as:

- Section 4.8 of the current trial-approved version of the applicable SPC, supplied for use within the trial; (note this may not necessarily be the latest version of the SPC and may be for a different brand of IMP).

19.2 Monitoring period for toxicity data

Toxicity will be monitored and reported (as per section 19.3) for patients **from the date of the first dose of ARIEL trial treatment until 4 weeks after the last ARIEL trial treatment**. Toxicity will be recorded using Common Toxicity Criteria for Adverse Events version 5.0 (CTCAE v5.0).

19.3 Reporting requirements

As the IMPs and non-IMPs in ARIEL are licensed products being used within licensed indication, with well documented safety profiles, the trial will only require expedited reporting (within 24 hours of the trial site becoming aware of the event) for SARs and SUSARs related to the trial IMPs (anti-EGFR agents). The following events will be collected:

Chemotherapy Alone Arm

- Adverse events (non-serious or serious) related to trial chemotherapy will be collected on the relevant treatment eCRFs. These events are not to be reported as SARs or SUSARs as they do not relate to the trial IMPs.

Chemotherapy Plus Anti-EGFR Agent Arm

- All ARs (any grade) related to anti-EGFR agent
- All SARs (any grade) related to anti-EGFR agent to be reported on the SAR/SUSAR eCRF
- All SUSARs (any grade) related to anti-EGFR agent to be reported on the SAR/SUSAR eCRFAdverse events (non-serious or serious) related to trial chemotherapy will be collected on the relevant treatment eCRFs. These events are not to be reported as SARs or SUSARs unless considered to also be related to the anti-EGFR agent.

SUSARs related to non-IMPs where there is a possibility of an interaction between the non-IMPs and the anti-EGFR agent must be reported as SUSARs (no need to report if related to non-IMP where no suspected interaction). SUSARs which might be linked to either non-IMP or anti-EGFR agent but cannot be attributed to only one must be reported as a SUSAR related to the anti-EGFR agent.

SARs and SUSARs (Chemotherapy plus anti-EGFR agent Arm only) must be reported on the SAR/SUSAR eCRF on the electronic database **within 24 hours** of the trial site team becoming aware of the event. SARs and SUSARs will be actively monitored and reported **from the date of the first anti-EGFR dose** until 4 weeks after the last ARIEL trial treatment.

If the site team becomes aware of any SARs or SUSARs after this active monitoring period, these should also be reported. (Participants on the Chemotherapy Alone Arm are not administered any IMPs as part of this trial therefore SARs and SUSARs are not applicable to these participants).

Non-serious or serious AEs not related to anti-EGFR agents or trial chemotherapy will not be collected for trial purposes, but must still be recorded in the participants' medical notes.

19.4 Responsibilities

Principal Investigator (PI):

1. Checking for ARs when participants attend for treatment / follow-up.
2. Using medical judgement in assigning seriousness and causality using the relevant Reference Safety Information approved for the trial.
3. Ensuring that all SARs (including SUSARs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SARs (including SUSARs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness and expectedness of SARs where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

CTRU:

1. Central data collection and verification of ARs, SARs and SUSARs according to the trial protocol onto a MACRO database.
2. Using the RSI to assign expectedness of all SARs

3. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Expedited reporting of SUSARs to the MHRA, REC and Sponsor within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing annual Development Safety Update Reports (DSUR) for the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC):

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

20 Endpoints

20.1 Primary endpoint:

The primary endpoint is early tumour shrinkage (ETS), measured 8 weeks after the start of treatment. This is taken as a binary variable with ETS defined as a 30% or greater reduction in the sum of maximum diameters (SMD) of RECIST target lesions when compared with the SMD recorded at baseline.

20.2 Secondary endpoints:

- Depth of response at 16 weeks from start of treatment, measured as the maximum tumour shrinkage observed in a patient compared with baseline. This will be taken as a continuous measure.
- Overall Treatment Utility (OTU, defined in Appendix D), assessed at 8 weeks from start of treatment. This is based on responses by clinician and participant regarding whether they were glad they gave or received their treatment allocation. OTU is scored as good, intermediate or poor, dependent on subjective measures of benefit or harm.
- Overall survival (OS), measured from time of randomisation to death from any cause.
- Patient-reported HRQOL, measured using the EORTC QLQ-C30 and EORTC QLQ-CR29 disease specific module with additional items to cover anti-EGFR symptomatic toxicity using the EORTC-QLQ item library. This will be assessed at baseline, 8 weeks, 16 weeks and 12 months post-randomisation.
- Cost effectiveness, as summarised in Section 17.
- Toxicity, measured as described in Section 19 for the anti-EGFR treatment arm with further comparisons being made between the two treatment arms for the frequency and intensity of toxicity events.

20.3 Exploratory endpoint for translational research:

- Assessment of prognostic and predictive ability of other candidate biomarkers with regard to patient outcomes and anti-EGFR efficacy, including negative hyperselection by gene alterations in circulating tumour DNA (ctDNA) related to primary resistance to anti-EGFR therapy.

21 Statistical Considerations

21.1 Sample size

The study is powered to demonstrate that in EREG/AREG high patients with RAS-wt aCRC with right-PTL, administering anti-EGFR agents in addition to first-line chemotherapy provides an improvement in achievement of ETS compared to patients who receive chemotherapy alone.

Assuming that of the randomised patients who receive chemotherapy alone, 31% will achieve ETS while 57% will achieve ETS in the arm that receives anti-EGFR agents in addition to chemotherapy, **162 participants** would be required in order to provide 90% power and the 5% two-sided significance level. This is based on the likelihood ratio test and assumes that a 5% drop-out would be observed. This rate of ETS achievement in the arm that would receive chemotherapy alone is based on the results seen in the PRIME trial [44] for all patients with RAS-wt aCRC with right-PTL (treated with both chemotherapy alone and chemotherapy with anti-EGFR agents) and it is hypothesised that the group that receive anti-EGFR agents in addition to chemotherapy will achieve an equivalent outcome to patients with a left-PTL.

In addition to the EREG/AREG high patients, an observation group of EREG/AREG low patients will also be included within the trial, although these will not undergo randomisation and will all receive the same treatment (chemotherapy alone with no anti-EGFR agents). This observation group will receive the same number of patients as the EREG/AREG high group, taking the total number of patients to be biomarker tested for EREG/AREG to 324.

It is anticipated that of the patients registered to the trial, 125 will have a RAS/RAF -unknown status and will require RAS/RAF testing, thus 440 patients will be registered to the trial in order to achieve the 324 patients required in order to randomise the 162 EREG/AREG high patients. This is an initial estimate and may be changed based on observations made in Stage 2 of the trial, regarding proportion of patients that are EREG/AREG positive and negative.

21.2 Planned recruitment rates

The recruitment period is 3 years from up to 40 centres, with participants to be followed-up for 1 year minimum for longer-term outcomes. It is anticipated that 40 centres will be the amount required in order to recruit 11 patients per month. In order to assess the feasibility of biomarker delivery and the recruitment rate, an internal pilot phase has been included within the trial, the details of which are given in Section 8.1.1. This will also allow the assumptions regarding percentage of EREG/AREG high patients and number of patients with RAS/RAF -unknown status to be assessed.

Stage 1 of the trial aims to assess whether the results of the biomarker testing can be returned within an acceptable amount of time. This will be assessed based on the results from either the first 20 patients are registered or after 6 months of recruitment, whichever occurs later. If the biomarker testing time is deemed acceptable, recruitment will continue for the Stage 2 analysis, for which a total of 53 patients are expected to be randomised within 12 months. After the 12 months, the Stage 2 assessment will be made and the trial will either stop, continue with changes or continue as planned dependent on the level of recruitment that has

been achieved by this point, as defined in Section 8.1.1.1. If the recruitment is deemed acceptable to continue as planned from the Stage 2 analysis, then the trial will continue to Stage 3 where the primary endpoint will be assessed. For Stage 3 it is anticipated that 335 patients will be registered and 162 patients will be randomised, across the remaining 18 months of recruitment,

Considerations will also be made for the recruitment rate for participants that progress or die early; that is, within having their first two cycles of systemic anti-cancer therapy. It is preferred that these participants are replaced in the study for the assessment of the primary endpoint. This will also be the case for participants with the homozygous DPYD variant allele genotype and patients who have a serious acute co-morbidity that requires treatment to be stopped (e.g. when surgery is required for a non-PD related event). Efforts will therefore be made to ensure that this occurs with potential adjustments to be made to the recruitment rate to ensure the sample size is still reached. Numbers of early deaths and progressions will be monitored by the DMEC and TSC and adjustments will be made based on their recommendations.

22 Statistical Analysis

22.1 General considerations

Statistical analysis is the responsibility of the CTRU Statisticians. The analysis plan detailed below provides an overview of the analyses to be performed. A separate and fully detailed statistical analysis plan (SAP) will be written before any analyses are undertaken (separate DMEC and final SAPs) and in accordance with CTRU standard operating procedures.

All efficacy analyses will be performed on an intention-to-treat (ITT) basis, where participants will be included according to the treatment arm they were recruited/randomised to. Per-protocol (PP) analyses will be performed should there be a sufficient number of major protocol violators. Toxicity analyses will be performed on the safety population, where participants will be included according to the treatment they received. Analyses based on the safety population will first summarise participants according to their starting dose (i.e. treatment received in the first treatment cycle), but may also be summarised taking into account dose reductions, as deemed appropriate.

The ITT population will consist of all patients randomised into the trial who received at least one dose of their allocated treatment. In this population, patients will be grouped according to the treatment they were randomised to receive.

The PP population will consist of participants who are not classed as major protocol violators, as defined in the statistical analysis plan. Participants will be summarised according to the treatment received in the first treatment cycle.

All hypothesis tests will be two-sided and use a 5% significance level, unless specified otherwise.

22.2 Frequency of analysis

While no formal interim analyses are planned for this trial, the internal pilot phase of the trial will be considered at two individual stages before formal analysis of the primary and secondary endpoints is carried out. These stages will be analysed as summarise in Section 20.2.

An independent Data Monitoring and Ethics Committee (DMEC) will be established to monitor the safety, data and related ethics of the trial and to provide independent advice and recommendation, based on relevant expertise. The TMG and DMEC will report directly to an independent Trial Steering Committee (TSC) which will be set up to provide independent supervision of the trial. The first TSC and DMEC meeting will be a joint meeting prior to start of recruitment to agree the data to be presented and monitored at future meetings, Subsequent TSC and DMEC meetings will be held at least annually (or as required by trial progress).

22.3 Interim analyses and stopping rules

N.B. these are not formal interim analyses, primary and secondary endpoints will not be analysed until Stage 3 is reached.

22.3.1 Stage 1 Analysis

Stage 1 will assess the time taken for the biomarker results to be returned to site from initial sampling (date of consent). This will be assessed after either 20 patients have been registered or after 6 months since the start of recruitment, whichever occurs later. For this analysis, a mean, median, interquartile range and one-sided 90% confidence interval for this time will be calculated. This will also be calculated for the group of patients who do not have a RAS-wt test available at registration.

If the lower limit of the one-sided 90% confidence interval for the time to biomarker results being returned to site does not include 3 weeks **and** the lower limit of the one-sided 90% confidence for the time to biomarker results being returned to site for patients who did not have a RAS-wt test available does not include 3 weeks, the trial will not proceed to Stage 2 and it will be concluded that the biomarker assessment cannot be feasibly integrated into the clinical care pathway. Note that the estimates must be below the pre-specified limit for both estimates for the study to close.

At this time point other metrics will also be assessed to analyse trial conduct and feasibility, but these will not necessarily be used in the assessment of feasibility.

22.3.2 Stage 2 Analysis

Stage 2 will assess the recruitment of the trial across the first 18 months of the recruitment process. This analysis will be descriptive and will include the mean monthly recruitment rate (with 95% confidence intervals) and the proportion of EREG/AREG high and low subgroups (with 95% confidence intervals). The number of patients registered that have a RAS/RAF - unknown will also be assessed against the number originally assumed and if necessary, adjustments will be made to the recruitment target. The number of patients recruited will be assessed against the red, amber and green criteria, outlined in Section 8.1.1.1 and the trial will either stop, continue with changes or continue as planned accordingly.

22.4 Primary endpoint analysis

The primary analysis on ETS at 8 weeks from start of treatment will be conducted using a logistic regression model which will compare the probability of being an ETS responder in the two treatment groups, adjusting for the minimisation factors. Treatment and covariate estimates, standard errors, odds ratios, 95% confidence intervals and p-values will be presented for all variables incorporated in the model. The mean ETS and confidence intervals will be presented with the proportion of patients that are ETS responders and exact confidence intervals, by group. The final primary analysis for each randomisation will be after all participants have been followed up for their primary endpoint after 8 weeks and data is complete.

22.5 Secondary endpoint analysis

Depth of response (DpR) will be measured at 16 weeks from start of treatment. Median DpR will be measured and corresponding 95% confidence intervals (CIs) will be calculated. DpR will be compared between the two treatment groups using a linear regression model, adjusting for the minimisation factors. All model assumptions will be tested. Analysis will also be carried

out in order to assess the association between DpR and OS using a Cox proportional hazards model with DpR included as a covariate. The correlation between DpR will be assessed and a p-value will be calculated.

Overall treatment utility (OTU) will be measured at 8 weeks from the start of treatment and summarised by calculating the differences in rates between the treatment groups with corresponding 95% CIs. Treatment groups will be compared using ordered logistic regression to adjust for the minimisation factors.

For OS, Treatment groups will be compared using a Cox proportional hazards model to adjust for the minimisation factors. The assumptions of the Cox proportional hazards model will be tested. Participants who are still alive at the time of analysis, or who have come off trial prior to observing their death, will be censored at the last date they were known to be alive. Treatment groups will also be compared using the log-rank test statistic. The time to death will be presented using the Kaplan-Meier (KM) estimate of the survivor function. The median overall survival time and other relevant summaries will be estimated with corresponding 95% CIs.

Mean scores with corresponding 95% CIs will be calculated for all domains of the EORTC QLQ-C30 and CR29 for each treatment group and overall, at each follow-up time point. Change in mean score from baseline with 95% CIs will be reported at each follow-up time point. Treatment groups (where applicable) will be compared using a linear mixed effects regression model, adjusted for the minimisation factors, relevant clinical characteristics and baseline QoL scores. In order to evaluate the clinical significance of any observed differences between the treatment arms, the proportions of patients showing minimally clinically important improvement/deterioration will be considered, as per the published guidelines, and defined in the statistical analysis plan.

Cost-effectiveness will be analysed using the methods described in Section 0. This part of the analysis will be the responsibility of the Health Economist.

Patient acceptability will be summarised for all patients that refuse consent to registration and those that refuse to consent to randomisation having previously consented to registration. As this is assessed prior to randomisation this cannot be compared across treatment arms.

Safety and toxicity data will be measured for the anti-EGFR arm as described in Section 19. Summaries of SAEs, SARs, SUSARs, ARs and AEs will be created based on the safety population. To assess toxicity, the rate of CTCAE v5.0 grade ≥ 2 haematological and non-haematological toxicities, the maximum grade per participant for each toxicity and rates of toxicities overall and per cycle will be summarised descriptively for each treatment group. Individual SUSAR/SAR/SAE line listings will be reported by treatment received.

Further comparisons of the frequency and intensity of toxicity events will be carried out for both treatment arms. The toxicity events will be summarised and tabulated for both arms and overall.

22.6 Additional considerations

Analyses will be carried out to compare the performance of the randomised participants to the EREG/AREG low patients who are to be given standard of care and followed up at 12 months

post-randomisation. This analyses may include but are not limited to comparing survival at 12 months between the two groups and summaries of the Overall Response Rate (ORR), response at site level and number of progressions and deaths across the two groups.

23 Trial Monitoring

A trial monitoring plan will be developed and agreed by the Trial Management Group (TMG) and Trial Steering Committee (TSC) based on the trial risk assessment; this may include on site monitoring. Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the Consent Form.

CTRU will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

23.1 Data Monitoring and Ethics Committee

An Independent Data and Ethics Monitoring Committee (DMEC) will review the safety and ethics of the trial. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at at-least yearly intervals. The DMEC will also review any other external information deemed relevant to the ethical running of the study.

23.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However, missing data items will not be chased from participants (although missing questionnaires may be). The CTRU and Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

23.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the Trial Steering Committee and, where applicable, to individual NHS Trusts.

24 Quality Assurance Processes

24.1 Quality assurance

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research and through adherence to CTRU Standard Operating Procedures.

24.2 Serious breaches

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the Health Research Authority (HRA) Standard Operating Procedure) that they become aware of. A 'serious breach' is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

25 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, 1996. Informed written consent will be obtained from the patients prior to randomisation/registration into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

25.1 Ethical approval

The trial will be submitted to and approved by a REC and the appropriate Site Specific Assessor for each participating centre prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

26 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name, date of birth, NHS number, hospital number.
- appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- copies of participant consent forms, which will include participant names, will be sent to the CTRU when a participant is registered/randomised into the trial. Participant NHS number will be collected at baseline, but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as 'hard copy' scans or local blood results), the participant's name and other personal identifiable data must be obliterated by site before sending.
- where anonymisation/pseudonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

Assessment of efficacy will be performed at Leeds Teaching Hospital Trust by the trial radiology team. All information collected for this assessment will be kept strictly confidential. The Leeds Teaching Hospital Trust will comply with all aspects of the 2018 Data Protection Act. Information will be held securely at the Leeds Teaching Hospital Trust and data will be transferred by the completion of e-CRFs as part of the secure and user-restricted trial database.

If a participant withdraws consent from further trial treatment and / or further collection of data their data will remain on file and will be included in the final trial analysis.

27 Archiving

27.1 Trial data and documents held by CTRU

At the end of the trial, data and the Trial Master File will be securely archived by CTRU in line with the Sponsor's procedures for a minimum of 25 years.

27.2 Trial data and documents held by research sites

Site data and documents will be archived at the participating research sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

27.3 Participant medical records held by research sites

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

28 Statement of Indemnity

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

29 Trial Organisational Structure

29.1 Responsibilities

29.1.1 Individuals and individual organisations

Chief Investigators (CIs) – The CIs are involved in the design, conduct, co-ordination and management of the trial. The CIs will have overall responsibility for the design and set-up of the trial, and pharmacovigilance within the trial.

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU) – The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with the UK Policy Framework for Health and Social Care Research and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the UK Policy Framework for Health and Social Care Research including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support ethical approval submissions, any other site-specific approvals and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

29.1.2 Oversight and trial monitoring groups

Trial Management Group (TMG) – The TMG, comprising the CIs, CTRU team, other key external members of staff involved in the trial and a PPI representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the REC and HRA and supporting applications for Site Specific Assessments, (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Pathology Steering Group – (PSG) – The PSG, comprising the CIs, Pathology Lead, Translational Lead, representatives from the central laboratories and CTRU team will be responsible for overseeing the implementation and monitoring of the pathology and translational aspects of the trial. The Pathology Lead and Translational Lead are responsible for the pathology and EREG/AREG biomarker quality assurance, respectively and for the institutional release, movement, archiving and biobanking of biospecimens stored in their laboratories.

Trial Steering Committee (TSC) – The TSC, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a PPI representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Sponsor will be invited to TSC meetings. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) – The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment and the follow-up period. The Committee will meet annually as a minimum.

30 Publication policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigators, Trial Management Group members, trial leads and relevant senior CTRU staff meeting the criteria for authorship will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the DMEC and TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

An electronic copy of peer-reviewed, published papers arising from this research will be deposited in the Europe PubMed Central database.

31 Protocol Version History Log

Version number	Version Date	Summary of key changes
1.0	**3rd August 2021**	Original version.
2.0	**29th September 2021**	Updates made following comments received from the MHRA (CTA Notice of Non-Acceptance).
3.0	**25th October 2023**	Addition of ctDNA collection at registration and on completion of the trial treatment at 16 weeks. Clarification on pathology sample process - Minimum 5 scrolls to Birmingham (please do not send slide mounted sections) for AREG/EREG testing. Addition of wording to explain that consent will be sought prior to randomisation for the central collection of CT scans and that patient identifiers will be shared with Leeds Teaching Hospitals NHS Trust for central review. Removal of modified FOLXOXIRI as a standard chemotherapy regimen. Amendment to stage 2 of the internal pilot (section 8.1.1.1) Clarifications and minor administrative updates throughout relating to trial processes, addresses, and trial staff.

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Appendix A - WHO Performance Status

GRADE	WHO PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

Appendix B – Guidance on treatment with anti-EGFR agents

Note: For the purposes of the ARIEL trial both cetuximab and panitumumab are considered Investigational Medicinal Products (IMPs)

Treatment with cetuximab

From TA439:

Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with:

- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

Note TA439 does not allow the combination of cetuximab with capecitabine.

A typical regimen would be:

- Cetuximab is given by intravenous infusion once every 2 weeks at a dose of 500 mg/m^2 body surface area.
- Dose banding as per local protocol is permitted.
- Doublet chemotherapy (ie FU based with oxaliplatin or irinotecan) should be prescribed alongside anti-EGFR. This should be prescribed as per local guidelines.

This treatment should be delivered every 2 weeks, with safety assessments up to 72 hours beforehand.

Participants should be monitored closely during the infusion and for at least 1 hour after the end of the infusion, particularly during the first administration.

Either rescue or prophylactic antibiotics should be prescribed as a method to optimise the control of significant acneiform rash.

Treatment with panitumumab

Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with:

- FOLFOX or
- FOLFIRI.

Note TA439 does not allow the combination of panitumumab with capecitabine.

A typical regimen would be:

- Panitumumab is given by intravenous infusion once every 2 weeks at a dose of 6 mg/kg of body weight.
- Dose banding as per local protocol is permitted.
- Doublet chemotherapy (ie FU based with oxaliplatin or irinotecan) should be prescribed alongside anti-EGFR. This should be prescribed as per local guidelines.

This treatment should be delivered every 2 weeks, with safety assessments up to 72 hours beforehand.

Either rescue or prophylactic antibiotics should be prescribed as a method to optimise the control of significant acneiform rash.

Toxicities/side effects of cetuximab and panitumumab

Based on an analysis of patients receiving cetuximab/panitumumab monotherapy, the most commonly reported adverse reactions are skin reactions occurring in approximately 90% of patients. These reactions are related to the pharmacologic effects of panitumumab, and the majority are mild to moderate in nature with approximately 10% severe (grade 3 or higher, NCI-CTC). Except where indicated, the data describe adverse reactions reported from clinical studies in patients with metastatic colorectal carcinoma who received panitumumab as a single agent: Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA Organ System	Frequency	Undesirable Effect
Skin and subcutaneous tissue disorders	Very common (≥ 1/10)	Rash Erythema Skin exfoliation Pruritus Dry skin Skin fissures Paronychia
Gastrointestinal disorders		Diarrhoea
General disorders and administrative site conditions		Fatigue
General disorders and administrative site conditions	Common (≥ 1/100 to < 1/10)	Infusion reactions (pyrexia, chills)
Metabolism and nutrition disorders		Hypomagnesaemia Hypocalcaemia Hypokalaemia Dehydration
Gastrointestinal disorders		Nausea Vomiting
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough
Nervous system disorders		Headache
Eye disorders		Conjunctivitis Growth of eyelashes Increased lacrimation Ocular hyperaemia Dry eye Eye pruritus
Skin and subcutaneous tissue disorders		Stomatitis Mucosal inflammation Onycholysis Hypertrichosis Alopecia Nasal dryness Dry mouth

Hypersensitivity reactions:

About 3% of patients treated with cetuximab/panitumumab have experienced infusion-related reactions (this is slightly more common for cetuximab than panitumumab), including chills, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting, with most infusion reactions being mild to moderate (NCI-CTC grade ≤2) in severity. Severe infusion reactions (anaphylaxis, angioedema, bronchospasm, cardiorespiratory arrest and hypotension), occur in less than 1% of patients treated and, very rarely can be fatal.

- Anti-EGFR is, therefore, contraindicated in patients with a history of severe or life threatening hypersensitivity reactions.
- Serious infusion-related reactions are unpredictable and can occur suddenly. Panitumumab/cetuximab should be permanently discontinued if a severe or life threatening reaction occurs.
- In patients experiencing a mild or moderate infusion-related reaction, the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.
- Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported. Patients should be warned of the possibility of a late onset reaction, made aware of possible symptoms and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.

The below table provides suggested recommendations in case of allergic/hypersensitivity reaction and is relevant to cetuximab and panitumumab

CTC Grade **Allergic/hypersensitivity reaction**	**Treatment**
Grade 1 Transient flushing or rash, drug fever <38°C	Decrease the cetuximab/panitumumab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab/panitumumab could be doubled if required.
Grade 2 Rash; flusing;urticarial; dyspnoea; drug fever ≥38°C	Stop cetuximab/panitumumab infusion. Administer bronchodilators, oxygen etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 Grade 3: Symptomatic bronchospasm, with or without urticarial; parenteral medication(s) indicated; allergy-related oedema/angioedema; hypotension. Grade 4: Anaphylaxis	Stop cetuximab/panitumumab infusion immediately and disconnect infusion tubing from the patient. Administer adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen etc., as medically indicated. Patients have to be withdrawn immediately from treatment and must not receive any further cetuximab/panitumumab treatment.

Once the infusion rate has been slowed for an allergic reaction, it should remain at the slower rate for all subsequent infusions.

If the patient has a second allergic/hypersensitivity reaction on the slower infusion rate, the infusion should be stopped and no further cetuximab or panitumumab administered.

If a patient receives a grade 3 or 4 allergic/hypersensitivity reaction at any time, cetuximab or panitumumab must be discontinued.

If there is any doubt whether a reaction is an allergic/hypersensitivity reaction of Grades 1-4, the CI should be contacted immediately to discuss and grade the reaction.

Panitumumab/cetuximab dermatological toxicity

- Over 90% of patients treated with cetuximab/panitumumab in previous trials developed skin or nail side-effects, usually a mild-to-moderate acneiform rash, similar to that seen during cetuximab therapy. This reached NCI CTC Grade 3 in 4% and resulted in discontinuation of the drug in 1% of patients.
- All patients allocated to receive cetuximab/panitumumab should be forewarned that they are very likely to develop a rash. At the first development of a rash we recommend:
    - start an oral tetracyline, e.g lymecycline 408 mg b.d.
    - start topical emollients (e.g. E45®) and bath additives (e.g. Hydromol®)
- Dose modifications:
    - For CTC grade 1 or 2: continue treatment with cetuximab/panitumumab.
    - If a patient experiences grade 3 skin toxicity (rash effects > 50% of body surface area), cetuximab/panitumumab therapy may be delayed for up to 14 days without changing the dose level.
    - If grade 3 skin toxicity occurs for a second and third time, cetuximab/panitumumab therapy may again be delayed for up to 14 days with concomitant dose reductions to 80% and then 60%.
    - Cetuximab/ panitumumab dose reductions are permanent.
    - Patients must discontinue if more than 2 consecutive infusions are withheld or grade 3 skin toxicity occurs for a fourth time despite appropriate dose reduction.
    - If the toxicity resolves to grade 2 or less by the following treatment period, treatment may be resumed.

- Nail toxicities occur in 8% of patients with cetuximab/panitumumab, characterised by a paronychial inflammation with associated swelling of the lateral skin folds of toes and fingers, especially great toes and thumbs, which may be painful. It may persist for up to three months after cessation of anti-EGFR therapy

Cetuximab/panitumumab non-dermatological toxicity

The addition of anti-EGFR increases the incidence of nausea, vomiting and diarrhoea, particularly when delivered alongside chemotherapy.

- Hypomagnesemia has been reported in up to 65% of patients following cetuximab therapy.
    - Patients should have magnesium concentration monitored at baseline, prior to each cycle of chemotherapy and for up to 8 weeks after the last dose of chemotherapy, or until magnesium has normalised, whichever is the longer.
    - Hypomagnesemia should be corrected by intravenous supplementation if grade 3 (<0.4) or symptomatic, or oral supplementation if lesser degrees (grade 1 or 2).

- Diarrhoea grade 3/4 has been reported in approx. 6% of patients treated with cetuximab or panitumumab plus chemotherapy.
    - For diarrhoea occurring between cycles, treat symptomatically initially: loperamide 2-4mg qds and/or codeine phosphate 30-60 mg qds as required.
    - If diarrhoea has not resolved by the time the next cycle is due, delay 1 week.
    - If diarrhoea is a problem despite symptomatic treatment, or if more than one delay is required, reduce the chemotherapy (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
    - If further toxicity occurs reduce 5FU (bolus and infusion) and oxaliplatin/irinotecan doses by a further 20%.
    - If diarrhoea persists despite this dose reduction, further reduction of cetuximab or panitumumab should be considered.

<u>Cetuximab/panitumumab ophthalmological toxicity</u>

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

<u>Dose omissions and reductions</u>

- All patients should receive their first anti-EGFR treatment at the full dose. If this is tolerated with mild or moderate toxicity, the subsequent treatments should be administered at the same dose.
- Examples of reasons for withholding panitumumab or cetuximab are:
    - Symptomatic skin- or nail-related toxicity of a severity requiring strong analgesia, systemic steroids, intravenous antimicrobial therapy or surgical debridement
    - Symptoms felt to be intolerable by the patient
    - If the a dose of panitumumab/cetuximab has been withheld for toxicity, it may be reintroduced at the next cycle at 80% dose, provided the adverse event has improved to ≤ Grade 2, and systemic steroids, IV antibiotic or IV antifungal treatment are no longer required.
- Non-dermatological symptoms should be managed as per chemotherapy regimens (see suggested guidelines above). If the patient has severe non-dermatological toxicity to which, in the opinion of the investigator, cetuximab/panitumumab has contributed significantly, cetuximab/panitumumab should be withheld for the next cycle.
    - In this event, cetuximab/panitumumab may be re-introduced in the subsequent cycle at 80% dose, provided that the adverse event has improved to ≤ Grade 2

Appendix C – National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

Toxicities will be assessed based on the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

A copy of NCI-CTCAE is provided in the Investigator Site File and may be obtained at:
http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix D – Overall Treatment Utility (OTU) Definition

OTU is an emerging clinical outcome measure incorporating objective and participant reported measures of anticancer efficacy, tolerability and acceptability of treatment, assessed 8 weeks post-randomisation and condensed into a simple 3-point score.

OTU may be regarded as asking the clinician: *"With the benefit of hindsight, are you glad you gave this treatment?"* and asking the participant: *"With the benefit of hindsight, are you glad you received it?"*: OTU is scored as good, intermediate or poor, corresponding to "yes", "uncertain/disagree" or "no" replies to these questions.

To score OTU, the participant is assessed 8 weeks after randomisation, using the following criteria:

1. **Is the treatment considered to have helped?**

    a. Scored as “YES” if all the following apply:
    - No evidence of radiological progression using RECIST
    - No other clinician-assessed evidence of cancer progression[1]
    - No major deterioration in Global QOL[2]

    b. Scored as “NO” if any of the following apply:
    - Radiological progression using RECIST
    - Other clinician-assessed evidence of cancer progression
    - Major deterioration in Global QOL

2. **Is the treatment tolerable and acceptable?**

    a. Scored as “YES” if all of the following apply:
    - No hospitalisation for any toxicities suspected related to trial treatment
    - The patient’s response to the question *"How much has your treatment interfered with your normal daily activities?"* is not "Very much" or “quite a bit”.
    - The patient’s response to question *"How worthwhile do you think your treatment has been?"* is not "Not at all"

    b. Scored as “NO” if any of the following apply:
    - One or more hospitalisations for any toxicities suspected related to trial treatment
    - The patient’s response to the question *"How much has your treatment interfered with your normal daily activities?"* is "Very much" or “quite a bit”
    - The patient’s response to the question *"How worthwhile do you think your treatment has been?"* is "Not at all"

Scoring:

Good OTU:	Patient is alive and scores are “YES” for both 1 and 2.
Intermediate OTU:	Patient is alive and scores are “YES/NO” or “NO/YES”.
Poor OTU:	Scores are “NO” for both 1 and 2, or patient has died.

[1] Clear clinical evidence of cancer progression which has not been confirmed radiologically.
[2] A drop of 16 or more points in EORTC QLQ-C30 Global QL Subscale

Appendix E Contraception Guidance

Definition of women of childbearing potential:

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Acceptable methods of contraception:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
    - o oral
    - o intravaginal
    - o transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation 1:
    - o oral
    - o injectable
    - o implantable [2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2],[3]
- sexual abstinence [4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception].