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A trial assessing preoperative chemotherapy in patients with locally advanced but operable colon cancer

Submission date
24/05/2021

Recruitment status
Recruiting

Registration date
28/09/2021

Overall study status
Ongoing

Last Edited
14/08/2024

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
After lung cancer, bowel (colorectal) cancer is the next most common cause of cancer death in the UK. Doctors usually treat bowel cancer with surgery often followed by chemotherapy to help stop the cancer from coming back. Despite all of the medical advances in recent years, until recently there have been no significant improvements to this treatment approach. However, an international research trial (FOxTROT 1) carried out in the UK, Denmark and Sweden, showed that having some chemotherapy (using the normal chemotherapy drugs for bowel cancer) before surgery (known as neoadjuvant chemotherapy), was safe and reduced the chances of the cancer coming back. However, patients in this study were mainly young and fit. Thanks to funding from Yorkshire Cancer Research, this important study will now be extended to see whether the same procedure is effective with gentler neoadjuvant chemotherapy before surgery in older patients or those with other medical problems (FOxTROT 2). This will be compared to the standard treatment of surgery first. FOxTROT 3 is a trial for younger, fitter patients. FOxTROT 4 (supported by Merck and Pierre Fabre) is a trial for people with a genetic mutation called BRAF. FOxTROT 5 (supported by GSK) is a trial for older patients or those with other medical problems whose tumour has an abnormality called deficient mismatch repair (dMMR).

Who can participate?
Patients who are at least 18 years old and have locally advanced but operable colon (bowel) cancer. Patients who are older and less fit will be considered for FOxTROT 2 and FOxTROT 5. Patients who are younger and fitter will be considered for FOxTROT 3. Patients with a genetic mutation called BRAF may be considered for FOxTROT 4. The patient's oncologist will decide which trial the patient is suitable for.

What does the study involve?
Patients will receive either the new approach (neoadjuvant treatment) or standard treatment. Patients allocated to the new approach will have neoadjuvant treatment (duration varies depending on the trial in which the patient is taking part) then a 3-to-4-week rest period. Then they will have an operation to remove the tumour. Patients allocated to standard treatment will

have their operation first. For all patients there will then be a 4-to-8-week recuperation period after surgery to allow for recovery. Depending on the trial the patient is recruited to, they will then be offered further trial treatment or transfer to standard care.

What are the possible benefits and risks of participating?
There is no guarantee that participants will benefit from the treatment given in this study. The chemotherapy given before surgery in FOxTROT 2 and FOxTROT 3 is the same as that given in standard care (just given before surgery, rather than after surgery). Patients may be more likely to have chemotherapy as part of their cancer treatment if given before surgery, rather than after surgery (current usual treatment). This was the case for patients in the FOxTROT 1 trial. FOxTROT 1 also showed that patients tended to have fewer complications after the operation if they had chemotherapy first.
There is a small risk that the tumour may continue to grow whilst receiving the treatment and the patient may need to have an emergency operation or stent. There is a risk of severe side effects from the treatment that may mean that the surgery is delayed, or that the patient may not be fit enough for an operation. However, the side effects of the chemotherapy given are well known and will be closely monitored by the medical team.

Where is the study run from?
Clinical Trials Research Unit (CTRU) at the University of Leeds (UK)

When is the study starting and how long is it expected to run for?
December 2020 to August 2029

Who is funding the study?
1. Yorkshire Cancer Research (UK)
2. Merck (Germany)
3. Pierre Fabre (France)
4. GSK (UK)

Who is the main contact?
Dr Lucy Bailey, FOxTROT@leeds.ac.uk
Mrs Claire Dimbleby, FOxTROT@leeds.ac.uk (FOxTROT 4)

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-chemotherapy-before-surgery-for-bowel-cancer-in-older-people-foxtrot-2
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-2-combinations-of-chemotherapy-for-bowel-cancer-foxtrot-3

Study website
https://ctru.leeds.ac.uk/foxtrot/

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2021-002216-31

IRAS number
1003812

ClinicalTrials.gov number
NCT06293625 - France only

Secondary identifying numbers
MO21/126572, CPMS 49772, IRAS 1003812

Study information

Scientific Title
FOxTROT: personalising neo-adjuvant chemotherapy in locally advanced but operable colon cancer

Acronym
FOxTROT

Study objectives
The overall aim of the FOxTROT trial platform is to refine and personalise the use of the neoadjuvant chemotherapy pathway in locally advanced operable colon cancer. As well as testing new clinical hypotheses within the platform, molecular stratification from diagnostic tissue will create future opportunities to test targeted novel agents with proven efficacy and safety in colon cancer.

FOxTROT 2: The alternative hypothesis is that the proportion of patients alive and disease-free at 3 years after randomisation treated with neoadjuvant chemotherapy (OxFp) is superior compared to those going straight to surgery. The null hypothesis in that there is no difference is the proportion of patients alive and disease-free at 3 years after randomisation.

FOxTROT 3: The alternative hypothesis is that the distribution of the tumour regression grade at the time of surgery allocated to mFOLFOXIRI is superior compared to those allocated to OxFp. The null hypothesis in that there is no difference in tumour regression grade (TRG).

(added 17/10/2023):
FOxTROT 4: The alternative hypothesis is that 6 weeks of neoadjuvant treatment with the EC

doublet will be safe and result in significant tumour regression compared with 6 weeks of neoadjuvant oxaliplatin and fluoropyrimidine (OxFp) chemotherapy.

(added 14/08/2024)
FOxTROT 5: The alternative hypothesis is that in older and/or frail patients with untreated locally advanced dMMR/MSI-H CC, 12 weeks of neoadjuvant dostarlimab (an anti-PD1 monoclonal antibody) prior to surgery with curative intent, followed by 36 weeks of post-operative dostarlimab, will demonstrate similar efficacy to that seen in younger and fitter populations.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 22/11/2021, Oxford-A Research Ethics Committee (Level 3, Block B, Whitefriars, Bristol, BS1 2NT, United Kingdom; +44 (0)207 1048206; oxforda.rec@hra.nhs.uk), ref: 21/SC/0277

Study design
Stratified multi-arm multi-site randomized trial platform

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Locally advanced but operable colon cancer

Interventions
Current interventions as of 14/08/2024:

FOxTROT is a stratified, multi-arm, multi-site randomised trial platform for patients with locally advanced but operable colon cancer. Prior to the initial registration period, all patients will have been assessed at a colon cancer MDT for review of pathology and radiology and potential participants will be identified. Patients meeting the registration eligibility criteria will be registered and a decision will be made about which FOxTROT comparison is most suitable. Participants will then be randomised in the appropriate comparison.

FOxTROT 2 randomises participants between two trial arms:
1. Straight to surgery: patients will proceed straight to surgery as soon as possible and will be

assessed for adjuvant chemotherapy as standard care.
2. Neoadjuvant chemotherapy followed by surgery. Participants in this arm will receive 6 weeks of OxFP chemotherapy with a choice (non-randomised) between two regimens: OxMdG (2-weekly oxaliplatin/calcium folinate/infusional fluorouracil) or OxCap (3-weekly oxaliplatin with capecitabine). These should be delivered as per local practice. The clinician has two options of initial dosing as described above: full dose OxFp, or 80% dose OxFp. Treatment should start as soon as possible following randomisation. Patients should be reviewed prior to each cycle of treatment to assess for toxicity and any evidence of disease progression.
Following the completion of neoadjuvant chemotherapy, all participants will be reviewed in the oncology clinic to be assessed for adjuvant chemotherapy.

FOxTROT 3 randomises participants between two trial arms:
1. In the control arm, Neoadjuvant chemotherapy (NAC) consists of 6 weeks of standard OxFp with a choice (non-randomised) of either OxMdG (2-weekly oxaliplatin/calcium folinate /infusional fluorouracil) or OxCap (3-weekly oxaliplatin with capecitabine).
2. In the experimental arm, NAC comprises three 2-weekly cycles of mFOLFOXIRI (oxaliplatin, irinotecan, calcium folinate, then a 46-hour infusion of fluorouracil).

For both arms, treatment should start as soon as possible following randomisation. Patients will receive postoperative adjuvant chemotherapy (AC) of either 6 or 18 weeks, bringing the total NAC/AC duration to 3 or 6 months respectively. In the control arm, AC is with OxFp; in the experimental arm AC may be either mFOLFOXIRI or OxFp.

FOxTROT 4 randomises participants between two trial arms:
1. In the control arm, NAC consists of 6 weeks of standard OxFp with a choice (non-randomised) of either OxMdG (2-weekly oxaliplatin/calcium folinate/infusional fluorouracil) or OxCap (oxaliplatin and capecitabine).
2. In the experimental arm, Neoadjuvant systemic anti-cancer therapy (NA SACT) comprises three 2-week cycles of cetuximab and encorafenib once daily (EC). Treatment should start as soon as possible following randomisation. Postoperative adjuvant treatment will be as per local practice.

FOxTROT 5 is a single-arm study and all participants will receive 12 weeks (a maximum of four, 3-weekly cycles; 500 mg IV on day 1 of each cycle) of preoperative dostarlimab and 36 weeks (a maximum of six, 6-weekly cycles; 1000 mg IV on day 1 of each cycle) of postoperative dostarlimab. Treatment should start as soon as possible following enrolment.

Participants will be randomised or enrolled using a central automated 24-hour internet service based at the Leeds Clinical and Translational Research Unit (CTRU).

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Previous interventions as of 17/10/2023:

FOxTROT is a stratified, multi-arm, multi-site randomised trial platform for patients with locally advanced but operable colon cancer. Prior to the initial registration period, all patients will have been assessed at a colon cancer MDT for review of pathology and radiology and potential participants will be identified. Patients meeting the registration eligibility criteria will be registered and a decision will be made about which FOxTROT comparison is most suitable. Participants will then be randomised in the appropriate comparison.

FOxTROT 2 randomises participants between two trial arms:
1. Straight to surgery: patients will proceed straight to surgery as soon as possible and will be

assessed for adjuvant chemotherapy as standard care.
2. Neoadjuvant chemotherapy followed by surgery. Participants in this arm will receive 6 weeks of OxFP chemotherapy with a choice (non-randomised) between two regimens: OxMdG (2-weekly oxaliplatin/calcium folinate/infusional fluorouracil) or OxCap (3-weekly oxaliplatin with capecitabine). These should be delivered as per local practice. The clinician has two options of initial dosing as described above: full dose OxFp, or 80% dose OxFp. Treatment should start as soon as possible following randomisation. Patients should be reviewed prior to each cycle of treatment to assess for toxicity and any evidence of disease progression.
Following the completion of neoadjuvant chemotherapy, all participants will be reviewed in the oncology clinic to be assessed for adjuvant chemotherapy.

FOxTROT 3 randomises participants between two trial arms:
1. In the control arm, Neoadjuvant chemotherapy (NAC) consists of 6 weeks of standard OxFp with a choice (non-randomised) of either OxMdG (2-weekly oxaliplatin/calcium folinate /infusional fluorouracil) or OxCap (3-weekly oxaliplatin with capecitabine).
2. In the experimental arm, NAC comprises three 2-weekly cycles of mFOLFOXIRI (oxaliplatin, irinotecan, calcium folinate, then a 46-hour infusion of fluorouracil).

For both arms, treatment should start as soon as possible following randomisation. Patients will receive postoperative adjuvant chemotherapy (AC) of either 6 or 18 weeks, so bringing the total NAC/AC duration to 3 or 6 months respectively. In the control arm, AC is with OxFp; in the experimental arm AC may be either mFOLFOXIRI or OxFp.

FOxTROT 4 randomises participants between two trial arms:
1. In the control arm, NAC consists of 6 weeks of standard OxFp with a choice (non-randomised) of either OxMdG (2-weekly oxaliplatin/calcium folinate/infusional fluorouracil) or OxCap (oxaliplatin and capecitabine).
2. In the experimental arm, Neoadjuvant systemic anti-cancer therapy (NA SACT) comprises three 2-week cycles of cetuximab and encorafenib once daily (EC). Treatment should start as soon as possible following randomisation. Postoperative adjuvant treatment will be as per local practice.

Participants will be randomised using a central automated 24-hour internet service based at the Leeds Clinical and Translational Research Unit (CTRU).

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Previous interventions:

FOxTROT is a stratified, multi-arm, multi-site randomised trial platform for patients with locally advanced but operable colon cancer. All patients will have been assessed at a colon cancer MDT for review of pathology and radiology and potential participants will be identified. Patients meeting the registration eligibility criteria will be registered and a decision will be made about which FOxTROT comparison is most suitable. Participants will then be randomised in the appropriate comparison.

FOxTROT 2 randomises participants between two trial arms:
1. Straight to surgery: patients will proceed straight to surgery as soon as possible and will be assessed for adjuvant chemotherapy as standard care.
2. Neoadjuvant chemotherapy followed by surgery. Participants in this arm will receive 6 weeks of OxFP chemotherapy with a choice (non-randomised) between two regimens: OxMdG (2-weekly oxaliplatin/calcium folinate/infusional fluorouracil) or OxCap (3-weekly oxaliplatin with

capecitabine). These should be delivered as per local practice. The clinician has two options of initial dosing as described above: full dose OxFp, or 80% dose OxFp. Treatment should start as soon as possible following randomisation. Patients should be reviewed prior to each cycle of treatment to assess for toxicity and any evidence of disease progression.

Following the completion of neoadjuvant chemotherapy, all participants will be reviewed in the oncology clinic to be assessed for adjuvant chemotherapy.

Participants will be randomised using a central automated 24-hour internet service based at the Leeds Clinical and Translational Research Unit (CTRU).

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
FOxTROT 2: Oxaliplatin, calcium folinate, infusional fluorouracil, capecitabine; FOxTROT 3: Irinotecan, Oxaliplatin, calcium folinate, Fluorouracil, Capecitabine; FOxTROT 4: Oxaliplatin, calcium folinate, infusional fluorouracil, capecitabine, Cetuximab, Encorafenib; FOxTROT 5: Dostarlimab.

Primary outcome measure
FOxTROT 2: Disease-free survival (DFS), defined as the time from randomisation to disease recurrence, treatment failure, or death from any cause. The date of recurrence will be taken as the date of the CT scan which concluded disease recurrence. If a CT scan is not carried out, the date of recurrence will be taken as the date of the sample which indicated disease recurrence. Individuals who are lost to follow-up or are alive and disease-free at the time of analysis will be censored at their last date known to be alive and disease-free.

FOxTROT 3: Tumour regression grade (TRG) (categorised as no response, mild, moderate, marked and complete response), measured at the time of surgery according to the modified Dworak grading system. DFS will be defined as per the FOxTROT 2 primary endpoint.

(added 17/10/2023)
FOxTROT 4: Tumour regression grade (TRG) categorised as response or no response, measured at the time of surgery according to the modified Dworak grading system, where response includes the subcategories mild, moderate, marked and complete response.

(added 14/08/2024)
FOxTROT 5: Proportion of participants with a pathological complete response in the resected tumour following neoadjuvant dostarlimab.

Secondary outcome measures
Current secondary outcome measures as of 14/08/2024:

Applicable to FOxTROT 2, FOxTROT 3, FOxTROT 4 and FOxTROT 5, where not part of the primary outcome measures:
1. Tumour regression grade (TRG) measured according to the modified Dworak grading system at the time of surgery
2. Tumour regression score (TRS) (categorised as poor/no response, partial, near complete and complete response), measured at the time of surgery
3. Histopathological endpoints, measured from pathological samples at the time of surgery:
3.1. Tumour cell density
3.2. Maximum tumour size
3.3. Depth of invasion
3.4. Apical node involvement
3.5. Peritoneal involvement
3.6. Nodal involvement
3.7. R1/R2 resection rates
4 Short-term efficacy (and association with longer-term outcomes):
4.1. Downstaging by T-stage, measured at pre-registration, post- neoadjuvant treatment (NAT) and 3-years post randomisation
4.2. Minimal residual disease by ctDNA and ctDNA alterations during NAT measured from blood samples collected at baseline, prior to each cycle of NAT, post-NAT and prior to adjuvant therapy
5. Safety and toxicity (treatment related) defined as the adverse reactions (ARs or irARs) and serious adverse events (SAEs) (including serious adverse reactions (SARs) and serious unexpected serious adverse reactions (SUSARs)) reported on the trial according to CTCAE v5.0 and Clavien-Dindo.
6. Cancer-related survival, defined as the time from randomisation to death caused by the same cancer, whether due to the original tumour or to a second primary same cancer. Individuals who are lost to follow-up or are still alive at the time of analysis will be censored at their last date known to be alive. Death not related to cancer will be specified as a competing risk.
7. Overall survival, defined as the time from randomisation to death from any cause. Individuals who are lost to follow-up or are still alive at the time of analysis will be censored at their last date known to be alive.
8. Surgical morbidity, defined as any surgery-related complication within 30 days post-surgery and surgical mortality, defined as death from any cause within 30 days post-surgery.
9. Patient-reported outcomes (PROs) assessed according to outcomes measured on the EQ-5D5L and QLQ-C30 and CR29. PROs will be collected at timepoints defined according to the protocol.
10. Geriatric assessment scoring, will be determined by the collection of domains used to assess frailty, full details of which are provided in the FOxTROT 2 protocol. Geriatric assessment data will be collected at baseline, and prior to adjuvant treatment – FOxTROT 2 and FOxTROT 5 only
11. Disease-free survival (DFS)

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Previous secondary outcome measures as of 17/10/2023 to 14/08/2024:
1. Tumour regression grade (TRG) measured according to the modified Dworak grading system at the time of surgery – FOxTROT 2 only
2. Tumour regression score (TRS) (categorised as poor/no response, partial, near complete and complete response), measured at the time of surgery – FOxTROT 2, FOxTROT 3 & FOxTROT 4
3. Histopathological endpoints, measured from pathological samples at the time of surgery – FOxTROT 2, FOxTROT 3 & FOxTROT 4:
3.1. Tumour cell density
3.2. Maximum tumour size
3.3. Depth of invasion
3.4. Apical node involvement

3.5. Peritoneal involvement
3.6. Nodal involvement
3.7. R1/R2 resection rates
4. Short-term efficacy (and association with longer-term outcomes) – FOxTROT 2, FOxTROT 3 and FOxTROT 4:
4.1. Downstaging by T-stage, measured at pre-registration, post-NAC and 3-years postrandomisation
4.2. Minimal residual disease by ctDNA and ctDNA alterations during neoadjuvant chemotherapy (NAC), measured from blood samples collected at baseline, prior to each cycle of NAC, post-NAC and prior to adjuvant chemotherapy
5. Safety and toxicity (both surgical and chemotherapy-related) defined as the adverse reactions (ARs) and serious adverse events (SAEs) (including serious adverse reactions (SARs) and serious unexpected serious adverse reactions (SUSARs)) reported on the trial according to CTCAE v5.0 and Clavien-Dindo – FOxTROT 2, 3 and 4
6. Cancer-related survival, defined as the time from randomisation to death caused by the same cancer, whether due to the original tumour or to a second primary same cancer. Individuals who are lost to follow-up or are still alive at the time of analysis will be censored at their last date known to be alive. Death not related to cancer will be specified as a competing risk – FOxTROT 2, FOxTROT 3 and FOxTROT 4
7. Overall survival, defined as the time from randomisation to death from any cause. Individuals who are lost to follow-up or are still alive at the time of analysis will be censored at their last date known to be alive – FOxTROT 2, FOxTROT 3 and FOxTROT 4
8. Surgical morbidity, defined as any surgery-related complication within 30 days post-surgery and surgical mortality, defined as death from any cause within 30 days post-surgery – FOxTROT 2, FOxTROT 3 and FOxTROT 4
9. Patient-reported outcomes (PROs) assessed according to outcomes measured on the EQ-5D5L and QLQ-C30 and CR29. PROs will be collected at baseline, post-NAC, prior to adjuvant chemotherapy, 12 months post-randomisation and 3 years post-randomisation – FOxTROT 2,
10. Geriatric assessment scoring, will be determined by the collection of domains used to assess frailty, full details of which are provided in the FOxTROT 2 protocol. Geriatric assessment data will be collected at baseline, and prior to adjuvant chemotherapy – FOxTROT 2 only
11. Disease-free survival (DFS) – FOxTROT 4

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Previous secondary outcome measures:

1. Tumour regression grade (TRG) measured according to the modified Dworak grading system at the time of surgery – FOxTROT 2 only
2. Tumour regression score (TRS) (categorised as poor/no response, partial, near complete and complete response), measured at the time of surgery – FOxTROT 2&3
3. Histopathological endpoints, measured from pathological samples at the time of surgery – FOxTROT 2&3:
3.1. Tumour cell density
3.2. Maximum tumour size
3.3. Depth of invasion
3.4. Apical node involvement
3.5. Peritoneal involvement
3.6. Nodal involvement
3.7. R1/R2 resection rates
4. Short-term efficacy (and association with longer-term outcomes) – FOxTROT 2 & 3:
4.1. Downstaging by T-stage, measured at pre-registration, post-NAC and 3-years post-

randomisation
4.2. Minimal residual disease by ctDNA and ctDNA alterations during neoadjuvant chemotherapy (NAC), measured from blood samples collected at baseline, prior to each cycle of NAC, post-NAC and prior to adjuvant chemotherapy
5. Safety and toxicity (both surgical and chemotherapy-related) defined as the adverse reactions (ARs) and serious adverse events (SAEs) (including serious adverse reactions (SARs) and serious unexpected serious adverse reactions (SUSARs)) reported on the trial according to CTCAE v5.0 and Clavien-Dindo – FOxTROT 2 & 3
6. Cancer-related survival, defined as the time from randomisation to death caused by the same cancer, whether due to the original tumour or to a second primary same cancer. Individuals who are lost to follow-up or are still alive at the time of analysis will be censored at their last date known to be alive. Death not related to cancer will be specified as a competing risk – FOxTROT 2 & 3
7. Overall survival, defined as the time from randomisation to death from any cause. Individuals who are lost to follow-up or are still alive at the time of analysis will be censored at their last date known to be alive – FOxTROT 2 & 3
8. Surgical morbidity, defined as any surgery-related complication within 30 days post-surgery and surgical mortality, defined as death from any cause within 30 days post-surgery – FOxTROT 2 & 3
9. Patient-reported outcomes (PROs) assessed according to outcomes measured on the EQ-5D-5L and QLQ-C30 and CR29. PROs will be collected at baseline, post-NAC, prior to adjuvant chemotherapy, 12 months post-randomisation and 3 years post-randomisation – FOxTROT 2 & 3
10. Geriatric assessment scoring, will be determined by the collection of domains used to assess frailty, full details of which are provided in the FOxTROT 2 protocol. Geriatric assessment data will be collected at baseline, and prior to adjuvant chemotherapy – FOxTROT 2 only

Overall study start date
01/12/2020

Completion date
01/08/2029

Eligibility

Key inclusion criteria
Current inclusion criteria as of 14/08/2024:
FOxTROT Registration Inclusion Criteria:
1. Biopsy-confirmed adenocarcinoma of the colon (or upper rectum if too high for radiotherapy); high-grade dysplasia is acceptable with unequivocal radiological evidence of invasive cancer*
2. Radiological stage T3-4, N0-2, M0
3. Patient being treated with curative intent
4. Tumour tissue is available for molecular testing (local or central)
5. Age ≥18 years at the time of registration
6. Patient able and willing to provide written informed consent for the study
* Patients with synchronous colonic tumours are eligible if the most advanced tumour meets the criteria above (please note MMR/MSI testing requirements for randomisation depending upon the location of the most advanced tumour)

FOxTROT 2 Inclusion Criteria:
1. Patients will be unsuitable for mFOLFOXIRI due to oncologist assessed frailty or comorbidity
2. Proficient mismatch repair (pMMR)/MSS tumour status for right sided tumours

3. Colorectal cancer (CRC) specialist-assessed fit to receive 6 weeks of NAC with OxFp (either full or modified dose) and surgery
4. Adequate full blood count: white blood cell (WBC) >3.0 x 10e9/l; platelets (PLTs) >100 x 10^9/l.
5. Anaemia (Hb <10.0 g/dl) is not an exclusion, but should be corrected by transfusion prior to
6. surgery and chemotherapy. If Hb remains low despite transfusions, surgery and chemotherapy can be given at the decision of the surgical and oncology teams.
7. Adequate renal biochemistry: glomerular filtration rate (GFR) >50 ml/min as assessed by local standards
8. Adequate hepatobiliary function: bilirubin <1.5 upper limit of normal (ULN) (patients with Gilbert's syndrome who have raised bilirubin but otherwise normal liver function tests are eligible for the study)
9. If female and of childbearing potential must agree to avoid pregnancy during and for 6 months after last dose of study treatment
10. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment
11. Signed the Informed Consent Document for randomisation

FOxTROT 3 Inclusion Criteria:
1. Patients need to be fit and suitable for mFOLFOXIRI. There is no fixed age cut-off, but most patients will be under 70 years.
2. pMMR/MSS tumour status for right sided tumours
3. Adequate full blood count: WBC >3.0 x10^9/l; Neutrophils ≥1.5 x10^9/l; Plts >100 x10^9/l. Anaemia (Hb < 100 g/l) is not an exclusion, but should be corrected by transfusion prior to surgery and chemotherapy. If Hb remains low despite transfusions, surgery and chemotherapy can be given at the decision of the surgical and oncology teams.
4. Adequate renal biochemistry: glomerular filtration rate (GFR) >50 ml/min as assessed by local standards
5. Adequate hepatobiliary function: bilirubin <1.5 upper limit of normal (ULN) (patients with Gilbert's syndrome who have raised bilirubin but otherwise normal liver function tests are eligible for the study)
6. If female and of childbearing potential must agree to avoid pregnancy during and for 6 months after last dose of study treatment
7. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment
8. Signed the Informed Consent Document for randomisation

FOxTROT 4 inclusion criteria:
1. pMMR/MSS colon adenocarcinoma (histologically confirmed).
2. Suitable for surgical resection and peri-operative SACT
3. No metastatic disease on routine staging investigations.
4. No prior treatment for bowel cancer
5. BRAFV600E mutation present in tumour biopsy (tested locally or centrally)
6. Adequate full blood count: WBC >3.0 x10^9/l; Neutrophils ≥1.5 x10^9/l; Plts ≥100 x10^9/l. Anaemia (Hb < 100 g/l) is not an exclusion but should be corrected by transfusion prior to surgery and SACT. If Hb remains low despite transfusions, surgery and SACT can be given at the decision of the surgical and oncology teams.
7. Adequate renal biochemistry: GFR >50 ml/min as assessed by local standards
8. Adequate hepatobiliary function: bilirubin < 1.5 x ULN (Patients with Gilbert's syndrome who have raised bilirubin, but otherwise normal liver function tests are eligible for the study.) AST /ALT <2.5 x ULN.

9. If female and of childbearing potential, must agree to avoid pregnancy during and for 6 months after the last dose of study treatment*
10. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 6 months after the last dose of study treatment*
11. Signed the Informed Consent Document for randomisation

FOxTROT 5 inclusion criteria:
1. Patients aged 70 years or more and/or with investigator-assessed frailty
2. dMMR and/or MSI-H tumour status by local or central assessment
3. Colon cancer specialist assessed fit to receive neoadjuvant dostarlimab and undergo surgery (refer to section 8.1 and Table 1 for guidance on assessing patient suitability for inclusion in FOxTROT 5)
4. Adequate full blood count: WBC >3.0 x109/l; Platelets >100 x109/l; neutrophils ≥1.5x109/l. Anaemia (Hb <9.0 g/dl) is not an exclusion but should be corrected by transfusion prior to commencement of study treatment. If Hb remains low despite transfusions, surgery and immunotherapy can be given at the discretion of the surgical and oncology teams
5. Adequate renal biochemistry: GFR ≥30 ml/min/1.73m2 for participants with serum creatinine (Cr) ≥1.5 x ULN OR Cr <1.5 x ULN
6. Adequate hepatobiliary function: Bilirubin ≤1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) AST/ALT ≤2.5 x ULN
7. For participants not taking warfarin: INR <1.5 or PT <1.5 x ULN and either PTT or aPTT <1.5 x ULN. Participants taking warfarin may be included on a stable dose with a therapeutic INR <3.5
8. If female and of childbearing potential, must agree to avoid pregnancy during and for 4 months after last dose of study treatment*
9. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 4 months after the last dose of study treatment*
10. Signed the Informed Consent Document for participation

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Previous inclusion criteria as of 17/10/2023 to 14/08/2024:
FOxTROT Registration Inclusion Criteria:
1. Biopsy-confirmed adenocarcinoma of the colon (or upper rectum if too high for radiotherapy); high-grade dysplasia is acceptable with unequivocal radiological evidence of invasive cancer*
2. Radiological stage T3-4, N0-2, M0
3. Patient being treated with curative intent
4. Tumour tissue is available for molecular testing (local or central)
5. Age ≥18 years at the time of registration
6. Patient able and willing to provide written informed consent for the study
* Patients with synchronous tumours are eligible if the most advanced tumour meets the criteria above (please note MMR/MSI testing requirements for randomisation depending upon the location of the most advanced tumour)

FOxTROT 2 Inclusion Criteria:
1. Patients will be unsuitable for mFOLFOXIRI due to oncologist assessed frailty or comorbidity
2. Proficient mismatch repair (pMMR)/MSS tumour status for right sided tumours
3. Colorectal cancer (CRC) specialist-assessed fit to receive 6 weeks of NAC with OxFp (either full or modified dose) and surgery
4. Adequate full blood count: white blood cell (WBC) >3.0 x 10e9/l; platelets (PLTs) >100 x 10^9/l.
5. Anaemia (Hb <10.0 g/dl) is not an exclusion, but should be corrected by transfusion prior to

6. surgery and chemotherapy. If Hb remains low despite transfusions, surgery and chemotherapy can be given at the decision of the surgical and oncology teams.
7. Adequate renal biochemistry: glomerular filtration rate (GFR) >50 ml/min as assessed by local standards
8. Adequate hepatobiliary function: bilirubin <1.5 upper limit of normal (ULN) (patients with Gilbert's syndrome who have raised bilirubin but otherwise normal liver function tests are eligible for the study)
9. If female and of childbearing potential must agree to avoid pregnancy during and for 6 months after last dose of study treatment
10. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment
11. Signed the Informed Consent Document for randomisation

FOxTROT 3 Inclusion Criteria
1. Patients need to be fit and suitable for mFOLFOXIRI. There is no fixed age cut-off, but most patients will be under 70 years.
2. pMMR/MSS tumour status for right sided tumours
3. Adequate full blood count: WBC >3.0 x10^9/l; Neutrophils ≥1.5 x10^9/l; Plts >100 x10^9/l. Anaemia (Hb < 100 g/l) is not an exclusion, but should be corrected by transfusion prior to surgery and chemotherapy. If Hb remains low despite transfusions, surgery and chemotherapy can be given at the decision of the surgical and oncology teams.
4. Adequate renal biochemistry: glomerular filtration rate (GFR) >50 ml/min as assessed by local standards
5. Adequate hepatobiliary function: bilirubin <1.5 upper limit of normal (ULN) (patients with Gilbert's syndrome who have raised bilirubin but otherwise normal liver function tests are eligible for the study)
6. If female and of childbearing potential must agree to avoid pregnancy during and for 6 months after last dose of study treatment
7. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment
8. Signed the Informed Consent Document for randomisation

FOxTROT 4 inclusion criteria
1. pMMR/MSS colon adenocarcinoma (histologically confirmed).
2. Suitable for surgical resection and peri-operative SACT
3. No metastatic disease on routine staging investigations.
4. No prior treatment for bowel cancer
5. BRAFV600E mutation present in tumour biopsy (tested locally or centrally)
6. Adequate full blood count: WBC >3.0 x10^9/l; Neutrophils ≥1.5 x10^9/l; Plts ≥100 x10^9/l. Anaemia (Hb < 100 g/l) is not an exclusion but should be corrected by transfusion prior to surgery and SACT. If Hb remains low despite transfusions, surgery and SACT can be given at the decision of the surgical and oncology teams.
7. Adequate renal biochemistry: GFR >50 ml/min as assessed by local standards
8. Adequate hepatobiliary function: bilirubin < 1.5 x ULN (Patients with Gilbert's syndrome who have raised bilirubin, but otherwise normal liver function tests are eligible for the study.) AST /ALT <2.5 x ULN.
9. If female and of childbearing potential, must agree to avoid pregnancy during and for 6 months after the last dose of study treatment*
10. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 6 months after the last dose of study

treatment*
11. Signed the Informed Consent Document for randomisation

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Previous inclusion criteria:
FOxTROT registration inclusion criteria:
1. Biopsy-confirmed adenocarcinoma of the colon (or upper rectum if too high for radiotherapy); high-grade dysplasia is acceptable with unequivocal radiological evidence of invasive cancer*
2. Radiological stage T3-4, N0-2, M0
3. Patient being treated with curative intent
4. Tumour tissue is available for mismatch repair (MMR)/microsatellite instability (MSI) testing (local or central)
5. No clinical or radiological evidence of bowel obstruction
6. Age ≥18 years at the time of registration
7. Patient able and willing to provide written informed consent for the study
* Patients with synchronous tumours are eligible if the most advanced tumour meets the criteria above (please note MMR/MSI testing requirements for randomisation depending upon the location of the most advanced tumour)

FOxTROT 2 inclusion criteria:
8. Patients will be unsuitable for mFOLFOXIRI due to oncologist assessed frailty or comorbidity
9. Proficient mismatch repair (pMMR)/MSS tumour status (for rt sided tumours)
10. Colorectal cancer (CRC) specialist-assessed fit to receive 6 weeks of NAC with OxFp (either full or modified dose) and surgery
11. Adequate full blood count: white blood cell (WBC) >3.0 x 10e9/l; platelets (PLTs) >100 x 10e9 /l. Anaemia (Hb <10.0 g/dl) is not an exclusion, but should be corrected by transfusion prior to surgery and chemotherapy. If Hb remains low despite transfusions, surgery and chemotherapy can be given at the decision of the surgical and oncology teams.
12. Adequate renal biochemistry: glomerular filtration rate (GFR) >50 ml/min as assessed by local standards
13. Adequate hepatobiliary function: bilirubin <1.5 upper limit of normal (ULN) (patients with Gilbert's syndrome who have raised bilirubin but otherwise normal liver function tests are eligible for the study)
14. If female and of childbearing potential must agree to avoid pregnancy during and for 6 months after study treatment
15. If male with a partner of childbearing potential, must agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment
16. Signed the Informed Consent Document for randomisation

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex

Both

Target number of participants

N=759 patients will be randomised into FOxTROT 2 , N=873 patients will be randomised into FOXTROT 3 , N=45 patients will be randomised into FOxTROT 4, N=62 patients will be enrolled into FOxTROT 5.

Key exclusion criteria

Current exclusion criteria as of 14/08/2024:

FOxTROT registration exclusion criteria:
1. Any patient for whom radiotherapy is advised by the multidisciplinary team (MDT)
2. Cases with a high index of suspicion of distant metastases or peritoneal nodules (cM1). However, cases with indeterminate abnormalities should be managed and investigated as per standard local MDT procedures and can be considered for trial entry if the MDT opinion is that these are considered most likely to be benign.
3. Colonic obstruction that has not been defunctioned*
4. Women who are pregnant or breastfeeding
* Obstructed patients cannot be included in the FOxTROT trials, unless the obstruction has been relieved. This would usually be by defunctioning. Patients may also be stented, but there is more limited safety data on this and these cases should be individually discussed with the Trial Management Group (TMG).

FOxTROT 2, FOxTROT 3 and FOxTROT 4 Exclusion Criteria:
1. Serious medical comorbidity, as assessed by the leading clinician (such as uncontrolled angina)
2. Any other malignant disease within the preceding 5 years with the exception of non-melanomatous skin cancer, carcinoma in situ and early-stage disease with a recurrence risk <10%
3. Known deficient mismatch repair (dMMR)/microsatellite Instability High (MSI-H) tumour status

FOxTROT 3 Additional Exclusion Criteria:
1. Known hypersensitivity to oxaliplatin, irinotecan or fluoropyrimidine therapy
2. Have a peripheral sensitive neuropathy with functional impairment
3. Have a severe chronic inflammatory bowel condition.
4. Known complete DPYD deficiency (homozygosity)
5. Recent or concomitant treatment with brivudine, sorivudine (or their chemically related analogues), St John’s Wort.

FOxTROT 4 Additional Exclusion Criteria:
1. Impending bowel obstruction
2. Known hypersensitivity to oxaliplatin, or fluoropyrimidine therapy
3. Prior treatment with any RAF or EGFR inhibitors
4. Have a peripheral sensitive neuropathy with functional impairment
5. Have a severe chronic inflammatory bowel condition.
6. Known complete DPYD deficiency (homozygosity)
7. Recent or concomitant treatment with brivudine, sorivudine (or their chemically related analogues), St John’s Wort.

FOxTROT 5 Exclusion Criteria:
1. Known pMMR or MSS/MSI-L colonic tumour status
2. Has a known additional malignancy that progressed or required active treatment within the past 2 years. Exceptions include adequately treated superficial skin cancers, superficial bladder cancers, and other in situ cancers

3. Is immunocompromised in the opinion of the investigator, is receiving any immunosuppressive medication, or has received systemic corticosteroids (>10mg prednisolone daily, or equivalent) within 7 days of first dose of study intervention. Use of inhaled steroids, local injection of steroids, topical steroids, and steroidal eye drops are allowed
4. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i. e. with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g. levothyroxine) is not considered a form of systemic treatment
5. Experienced any of the following with prior immunotherapy: any Grade 3 or higher immune-related adverse reaction (irAR), anygrade immune-related severe neurologic events (e.g. myasthenic syndrome/myasthenia gravis, encephalitis, Guillain-Barré syndrome, or transverse myelitis), any grade exfoliative dermatitis (Steven-Johnson syndrome, toxic epidermal necrolysis, or DRESS syndrome), any grade myocarditis. Non-clinically significant laboratory abnormalities are not exclusionary
6. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to enrolment
7. Has any history of interstitial lung disease or pneumonitis
8. Cirrhosis or unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal/gastric varices, or persistent jaundice
9. Has a history or current evidence of any medical condition, therapy, or laboratory abnormality that might confound the study results, interfere with their participation for the full duration of the study intervention, or indicate it is not in the best interests of the participant to participate, in the opinion of the investigator
10. Has a history of allogenic stem cell transplantation or organ transplantation
11. Has a history of congenital long QT syndrome
12. Has a history or evidence of cardiac abnormalities such as serious, uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities within the 6 months prior to enrolment
13. Is receiving any other anticancer or experimental therapy
14. Received a live vaccine within 30 days of planned start of study therapy
15. Has documented presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to enrolment
16. Has a positive hepatitis C virus (HCV) antibody test result at screening or within 3 months prior to enrolment. Note: Participants with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory HCV RNA test is obtained
17. Has a positive HCV RNA test result at screening or within 3 months prior to enrolment. Note: The HCV RNA test is optional and participants with negative HCV antibody test are not required to undergo HCV RNA testing as well
18. Is considered, in the investigator’s opinion, a poor medical risk due to severe, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring systemic therapy.
19. Has known history of human immunodeficiency virus (HIV) infection (unless the specific criteria in the FOxTROT 5 protocol are met)
20. A known history of severe allergic and/or anaphylactic reactions to chimeric, human or humanized antibodies, fusion proteins, or to dostarlimab or its excipients

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Previous exclusion criteria as of 17/10/2023 to 14/08/2024:

FOxTROT registration exclusion criteria:
1. Any patient for whom radiotherapy is advised by the multidisciplinary team (MDT)
2. Cases with a high index of suspicion of distant metastases or peritoneal nodules (cM1). However, cases with indeterminate abnormalities should be managed and investigated as per

standard local MDT procedures and can be considered for trial entry if the MDT opinion is that these are considered most likely to be benign.
3. Colonic obstruction that has not been defunctioned*
4. Women who are pregnant or breastfeeding
* Obstructed patients cannot be included in the FOxTROT trials, unless the obstruction has been relieved. This would usually be by defunctioning. Patients may also be stented, but there is more limited safety data on this and these cases should be individually discussed with the Trial Management Group (TMG).

FOxTROT 2, FOxTROT 3 and FOxTROT 4 Exclusion Criteria:
1. Serious medical comorbidity, as assessed by the leading clinician (such as uncontrolled angina)
2. Any other malignant disease within the preceding 5 years with the exception of non-melanomatous skin cancer, carcinoma in situ and early-stage disease with a recurrence risk <10%
3. Known deficient mismatch repair (dMMR)/microsatellite Instability High (MSI-H) tumour status

FOxTROT 3 Additional Exclusion Criteria:
1. Known hypersensitivity to oxaliplatin, irinotecan or fluoropyrimidine therapy
2. Have a peripheral sensitive neuropathy with functional impairment
3. Have a severe chronic inflammatory bowel condition.
4. Known complete DPYD deficiency (homozygosity)
5. Recent or concomitant treatment with brivudine, sorivudine (or their chemically related analogues), St John's Wort.

FOxTROT 4 Additional Exclusion Criteria:
1. Impending bowel obstruction
2. Known hypersensitivity to oxaliplatin, or fluoropyrimidine therapy
3. Prior treatment with any RAF or EGFR inhibitors
4. Have a peripheral sensitive neuropathy with functional impairment
5. Have a severe chronic inflammatory bowel condition.
6. Known complete DPYD deficiency (homozygosity)
7. Recent or concomitant treatment with brivudine, sorivudine (or their chemically related analogues), St John's Wort.

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Previous exclusion criteria:

FOxTROT randomisation exclusion criteria:
1. Any patient for whom radiotherapy is advised by the multidisciplinary team (MDT)
2. Strong evidence of distant metastases or peritoneal nodules (cM1), however patients with lung lesions of uncertain significance (<5 mm) are eligible
3. Peritonitis (secondary to perforated tumour)
4. Colonic obstruction that has not been defunctioned*
* Obstructed patients cannot be included in the FOxTROT trials, unless the obstruction has been relieved. This would usually be by defunctioning. Patients may also be stented, but there is more limited safety data on this and these cases should be individually discussed with the Trial Management Group (TMG).

FOxTROT 2 exclusion criteria:
5. Serious medical comorbidity, as assessed by the leading clinician (such as uncontrolled angina)

6. Any other malignant disease within the preceding 5 years with the exception of non-melanomatous skin cancer, carcinoma in situ and early-stage disease with a recurrence risk <10%
7. Known deficient mismatch repair (dMMR)/microsatellite Instability High (MSI-H) tumour status

Date of first enrolment
07/02/2022

Date of final enrolment
01/04/2027

Locations

Countries of recruitment
Australia

England

France

India

Netherlands

Scotland

Sweden

United Kingdom

Wales

Study participating centre
Airedale General Hospital
Skipton Rd
Steeton
Keighley
United Kingdom
BD20 6TD

Study participating centre
St Bartholomew's Hospital
W Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Ysbyty Gwynedd
Penrhosgarnedd
Bangor
United Kingdom
LL57 2PW

Study participating centre
Bradford Royal Infirmary
Duckworth Ln
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Calderdale Rotal Hospital and Huddersfield Royal Infirmary
Acre St
Lindley
Huddersfield
United Kingdom
HD3 3EA

Study participating centre
Addenbrooke's Hospital
Hills Rd
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
West Middlesex University Hospital
Twickenham Rd
Isleworth
United Kingdom
TW7 6AF

Study participating centre
Chesterfield Royal Hospital
Chesterfield Rd
Calow
Chesterfield

United Kingdom
S44 5BL

Study participating centre
Countess of Chester Hospital
Liverpool Rd
Chester
United Kingdom
CH2 1UL

Study participating centre
Darlington Memorial Hospital
Hollyhurst Rd
Darlington
United Kingdom
DL3 6HX

Study participating centre
Macclesfield District General Hospital
Victoria Rd
Macclesfield
United Kingdom
SK10 3BL

Study participating centre
Ipswich Hospital
Heath Rd
Ipswich
United Kingdom
IP4 5PD

Study participating centre
Conquest Hospital
The Ridge
Saint Leonards-on-Sea
United Kingdom
TN37 7RD

Study participating centre

Bensham Hospital
Fontwell Dr
Gateshead
United Kingdom
NE8 4YL

Study participating centre
Great Western Hospital
Marlborough Rd
Swindon
United Kingdom
SN3 6BB

Study participating centre
Basingstoke and North Hampshire Hospital
Aldermaston Rd
Basingstoke
United Kingdom
RG24 9NA

Study participating centre
Charing Cross Hospital and St Mary's
Fulham Palace Rd
London
United Kingdom
W6 8RF

Study participating centre
Kettering General Hospital
Rothwell Rd
Kettering
United Kingdom
NN16 8UZ

Study participating centre
St James's University Hospital
Beckett St
Harehills
Leeds
United Kingdom
LS9 7TF

Study participating centre
Queen Elizabeth Hospital & Lewisham Hospital
Stadium Rd
London
United Kingdom
SE18 4QH

Study participating centre
Royal Liverpool University Hospital
Prescot St
Liverpool
United Kingdom
L7 8XP

Study participating centre
Manchester Royal Infirmary
Oxford Rd
Manchester
United Kingdom
M13 9WL

Study participating centre
Crosshouse Hospital
Kilmarnock Rd
Crosshouse
Kilmarnock
United Kingdom
KA2 0BE

Study participating centre
Queen Margaret Hospital and Victoria Hospital
Whitefield Rd
Dunfermline
United Kingdom
KY12 0SU

Study participating centre

Forth Valley Royal Hospital
Stirling Rd
Larbert
United Kingdom
FK5 4WR

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Rd
Glasgow
United Kingdom
G12 0YN

Study participating centre
Royal Edinburgh Hospital
Morningside Pl
Edinburgh
United Kingdom
EH10 5HF

Study participating centre
Norfolk & Norwich University Hospital
Colney Ln
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
Hexham General Hospital
Corbridge Rd
Hexham
United Kingdom
NE46 1QJ

Study participating centre
Queen Alexandra Hospital
Cosham
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Royal Cornwall Hospital
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Royal Devon and Exeter Hospital
Barrack Rd
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal Free Hospital
Pond St
London
United Kingdom
NW3 2QG

Study participating centre
Royal United Hospital
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Weston Park Cancer Centre
Whitham Rd

Broomhall
Sheffield
United Kingdom
S10 2SJ

Study participating centre
St George's Hospital
Blackshaw Rd
London
United Kingdom
SW17 0QT

Study participating centre
Musgrove Park Hospital
Parkfield Dr
Taunton
United Kingdom
TA1 5DA

Study participating centre
The Christie
Wilmslow Rd
Manchester
United Kingdom
M20 4BX

Study participating centre
Clatterbridge Cancer Centre Liverpool and Clatterbridge Cancer Centre Wirral
Clatterbridge Rd,
Birkenhead
Wirral
United Kingdom
CH63 4JY

Study participating centre
The Royal Marsden Hospital (Chelsea and Sutton)
203 Fulham Rd
London
United Kingdom
SW3 6JJ

Study participating centre
Royal Surrey County Hospital
Egerton Rd
Guildford
United Kingdom
GU2 7XX

Study participating centre
Harrogate District Hospital
Lancaster Park Rd
Harrogate
United Kingdom
HG2 7SX

Study participating centre
Lincoln County Hospital
Greetwell Rd
Lincoln
United Kingdom
LN2 5QY

Study participating centre
UCL Cancer Institute
72 Huntley St
London
United Kingdom
WC1E 6DD

Study participating centre
Bristol Cancer Centre
22 Horfield Rd
Bristol
United Kingdom
BS2 8ED

Study participating centre
University Hospital Coventry
Clifford Bridge Rd
Coventry

United Kingdom
CV2 2DX

Study participating centre
Poole Hospital and Royal Bournemouth Hospital
Longfleet Rd
Poole
United Kingdom
BH15 2JB

Study participating centre
Royal Derby Hospital
Uttoxeter Rd
Derby
United Kingdom
DE22 3NE

Study participating centre
Royal Stoke University Hospital
Newcastle Rd
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
Derriford Hospital
Derriford Rd
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Leicester General Hospital
Gwendolen Rd
Leicester
United Kingdom
LE5 4PW

Study participating centre

Velindre Cancer Centre
Velindre Rd
Cardiff
United Kingdom
CF14 2TL

Study participating centre
Walsall Manor Hospital
Moat Rd
Walsall
United Kingdom
WS2 9PS

Study participating centre
Worcestershire Royal Hospital
Charles Hastings Way
Worcester
United Kingdom
WR5 1DD

Study participating centre
Royal Albert Edward Infirmary
Wigan Ln
Wigan
United Kingdom
WN1 2NN

Study participating centre
York Teaching Hospital
Wigginton Rd
Clifton
York
United Kingdom
YO31 8HE

Study participating centre
Dorset County Hospital
Williams Ave
Dorchester
United Kingdom
DT1 2JY

Study participating centre
Colchester Hospital
Turner Rd
Colchester
United Kingdom
CO4 5JL

Study participating centre
George Eliot Hospital
College St
Nuneaton
United Kingdom
CV10 7DJ

Study participating centre
University Hospital Monklands
Monkscourt Ave
Airdrie
United Kingdom
ML6 0JS

Study participating centre
University Hospital of North Tees
Hardwick Rd
Hardwick
Stockton-on-Tees
United Kingdom
TS19 8PE

Study participating centre
The James Cook University Hospital
Middlesbrough
United Kingdom
TS4 3BS

Study participating centre
Warwick Hospital
Lakin Rd

Warwick
United Kingdom
CV34 5BW

Study participating centre
East Yorkshire Hospitals NHS Trust (head Office)
Castle Hill Hospital
Castle Road
Cottingham
United Kingdom
HU16 5JQ

Study participating centre
Mid Cheshire Hospitals NHS Foundation Trust
Leighton Hospital
Leighton
Crewe
United Kingdom
CW1 4QJ

Study participating centre
Milton Keynes University Hospital
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre
University Hospital Crosshouse
Kilmarnock Road
Kilmarnock
United Kingdom
KA2 0BE

Study participating centre
Queen Margaret Hospital
Whitefield Road
Dunfermline
United Kingdom
KY12 0SU

Study participating centre
Victoria Hospital
Hayfield Road
Kirkcaldy
United Kingdom
KY2 5AH

Study participating centre
Ninewells Hospital
Ninewells Avenue
Dundee
United Kingdom
DD1 9SY

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE

Study participating centre
Singleton Hospital
Sketty Lane
Sketty
Swansea
United Kingdom
SA2 8QA

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Yeovil Hospital Bcsc
Yeovil District Hospital
Higher Kingston
Yeovil
United Kingdom
BA21 4AT

Study participating centre
Christian Medical College and Hospital (Local Sponsor for FOxTROT 2 only)
Brown Rd, CMC Campus
Ludhiana
India
141008

Study participating centre
CHU DIJON (Local Sponsor for FOxTROT 2 only)
1 Rue du Professeur Marion
Dijon
France
21000

Sponsor information

Organisation
University of Leeds

Sponsor details
Research & Innovation Centre
Leeds Teaching Hospitals NHS Trust
St James's University Hospital
Beckett Street
Leeds
England
United Kingdom
LS9 7TF
+44 (0)113 2060454
C.E.Skinner@leeds.ac.uk

Sponsor type
University/education

Website

http://www.leeds.ac.uk/

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Yorkshire Cancer Research

Alternative Name(s)
YCR

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Merck

Funder Name
Pierre Fabre

Funder Name
GSK

Results and Publications

Publication and dissemination plan
Planned publications in a high-impact peer-reviewed journal. The protocol is currently not available online.

Intention to publish date
01/08/2030

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.
CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.
The CTRU encourages a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.
The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

IPD sharing plan summary
Stored in non-publicly available repository, Available on request

Study outputs
Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No