Molecular selection of therapy in metastatic colorectal cancer: the FOCUS4 molecularly stratified RCT

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Scientific summary

FOCUS4 molecularly stratified RCT

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Scientific summary

Background

Approximately 16,000 people die from colorectal cancer (CRC) in the UK every year, making it the second most common cause of cancer death in the UK and accounting for 10% of all cancer deaths in the country. Given that the concept of one treatment for all patients with a particular type of cancer has become outdated, there is a need for a new approach to the design of clinical trials, allowing for the evaluation of multiple treatments in patients stratified based on biomarkers considered predictive of a treatment response. Prior to FOCUS4, the investigator team had successfully completed a feasibility study, FOCUS3, which showed that it was feasible to conduct complex biomarker-selected studies in the first-line setting in patients with metastatic colorectal cancer (mCRC). While FOCUS4 was being designed, molecular stratification of CRC revealed four major subgroups: microsatellite instability (MSI)-high cancer, owing to failure of the mismatch repair (MMR) mechanism (*c.* 4% of mCRC patients); *BRAF* mutation (*c.* 10% of mCRC patients), for which novel targeted drugs were being developed; *KRAS*/*NRAS* mutant (*c.* 45% of mCRC patients), an area of unmet clinical need; and the triple wild-type group (*BRAF*, *KRAS* and *NRAS* all wild type, *c.* 40%), for which epidermal growth factor receptor (EGFR) inhibitors were licensed for use in third-line therapy. We aimed to construct a platform that could evaluate novel therapies in these (and potentially other more novel) subgroups in parallel.

Objectives

The FOCUS4 trial was designed to enable the rapid evaluation of new agents to assess their clinical benefit in patient cohorts most likely to show benefit because of their molecular features. This trial was designed to characterise the tumours based on the presence of specific mutations or validated biomarkers and stratify eligible patients into comparison subtrials, which, by being a component of a large national study, would adapt efficiently to refinement of biomarker data and enable the rapid accrual of patients, despite the relative rarity of some molecular subgroups. Specifically, we aimed to answer the following questions:

- Clinical benefit. In the interval following standard first-line chemotherapy, do the proposed interventions improve progression-free survival (PFS) and eventually OS compared with a control group in the biomarker-defined cohorts?
    - In *BRAF*-mutant mCRC, does the combination of dabrafenib, panitumumab and trametinib increase PFS in the interval following first-line therapy in patients with stable or responding disease compared with active monitoring (FOCUS4-A)?
    - In *PIK3CA*-mutant/*PTEN*-loss mCRC, does aspirin improve PFS compared with placebo (FOCUS4-B)?
    - In the double-mutant *TP53* and *RAS* mutation subgroup, does the Wee1 inhibitor adavosertib (AstraZeneca Ltd, Cambridge, UK) improve PFS compared with active monitoring (FOCUS4-C)?
    - In the all wild-type subgroup (*KRAS*, *NRAS*, *PIK3CA* and *BRAF* wild type), does the pan Her inhibitor AZD8791 improve PFS compared with placebo (FOCUS4-D)?
    - In the unstratified group, does capecitabine monotherapy improve PFS compared with active monitoring (FOCUS4-N)?
- Improvement in trial design and conduct. What are the challenges and efficiencies of conducting a large, molecularly stratified platform trial in metastatic CRC in the UK health-care system?

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Design

FOCUS4 was an adaptive umbrella trial in mCRC that used the statistical methods of the multiarm, multistage randomised trial design. After registration and biomarker assessment during a 16-week standard first-line chemotherapy treatment, patients were stratified into one of four biologically defined cohorts (A to D). If stable or responding disease was confirmed at the end of 16 weeks, patients were then enrolled into the corresponding randomised trial of the novel targeted agent(s) or, for travel, logistic or technical reasons, to the one conventional chemotherapy maintenance trial (i.e. FOCUS4-N). Biomarker assessment was undertaken at two pathology centres (Leeds and Cardiff) and initially used reverse transcription polymerase chain reaction methods to assess the presence of *BRAF*, *KRAS*, *NRAS* and *PIK3CA* hotspot mutations, plus immunohistochemistry methods to detect MMR deficiency and *PTEN* loss. During the trial, the genetic technique was transferred onto a next-generation sequencing platform, which evaluated mutations in the whole gene of *BRAF*, *KRAS*, *NRAS*, *PIK3CA* and *TP53*.

Twenty subtrials were proposed by the trial group, five had full protocols prepared and three molecularly targeted subtrials and one unstratified subtrial were activated: FOCUS4-A (planned to evaluate dabrafenib, trametinib and panitumumab versus active monitoring in patients with *BRAF* mutant was not activated), FOCUS4-B (evaluated aspirin in the *PIK3CA*-mutant subgroup), FOCUS4-C (evaluated adavosertib in the *RAS* + *TP53* double-mutant subgroup) and FOCUS4-D (evaluated AZD8931 in the *BRAF-PIK3CA-RAS* wild-type subgroup). In addition, FOCUS4-N was active throughout and evaluated capecitabine monotherapy versus a treatment break in the unstratified group.

Setting and participants

FOCUS4 was carried out between January 2014 and October 2020, and included 1434 patients with locally advanced or mCRC registered from 88 hospitals in the UK. The setting selected for testing the novel agents, that is after 4 months of first-line chemotherapy, was new. Previous trials have shown that it is acceptable to have a treatment break after this time, and to recommence first-line chemotherapy if the disease is found to progress. This 'window of opportunity' allowed drugs to be assessed before the development of multiple mechanisms of drug resistance, as occurs in the last-line setting, with a relatively short time to event to enable rapid evaluation of the novel agents. Following the FOCUS4 trial interventions, patients were expected to restart first-line therapy and continue with standardly available treatment options. This window setting became more complex when EGFR inhibitors were approved for use in the UK as first-line treeament in *RAS* wild-type patients but with the stipulation that no interruption in treatment longer than 4 weeks was permitted.

Main outcome measures

The primary outcome measure for all subtrials was PFS measured from randomisation after the 4 months of first-line therapy comparing the intervention with active monitoring/placebo. At the close of the trial, feedback was elicited from all investigators through surveys and interviews, and was consolidated into a series of recommendations and lessons learned for the delivery of similar future trials.

Clinical benefit results

Between January 2014 and October 2020, 1434 patients were registered from 88 hospitals in the UK. Successful biomarker testing was completed in 1291 out of 1382 samples (93%), and 908 out of 1315

patients (69%) completing 16 weeks of first-line therapy were eligible for randomisation, with 361 randomly allocated into a subtrial:

- FOCUS4-A was not activated because the pharmaceutical company owning the agents showed unacceptable benefit/toxicity balance in their Phase I trials.
- FOCUS4-B evaluated aspirin in the *PIK3CA*-mutant/*PTEN*-overexpressed subgroup but recruited only six patients, so was closed for futility.
- FOCUS4-C evaluated adavosertib versus active monitoring in 67 patients in the *RAS* + *TP53* double-mutant subgroup and met its primary end point, showing an improvement in PFS [median 3.61 vs. 1.87 months; hazard ratio (HR) 0.35, 95% confidence interval (CI) 0.18 to 0.68; $p = 0.0022$]. This activity was clearly limited to patients with metastases from a primary tumour located in the left-sided colon and rectal cancers [left primary tumour location (PTL)], but not from the right side. Assessment of longer-term outcomes also showed an overall survival benefit with adavosertib compared with active monitoring in *RAS*-mutant and *TP53*-mutant patients with left PTL.
- FOCUS4-D evaluated AZD8931 in 32 patients in the *BRAF-PIK3CA-RAS* wild-type subgroup and showed no benefit so was discontinued after the first interim analysis.
- FOCUS4-N evaluated capecitabine monotherapy versus a treatment break in 254 unstratified patients and also met its primary end point showing improvement in PFS (HR 0.40, 95% CI 0.21 to 0.75; $p < 0.0001$).

Improvement in trial design and conduct

At the close of the trial, feedback was elicited from all investigators through surveys and interviews, and was consolidated into a series of recommendations and lessons learned for the delivery of similar future trials. Twenty recommendations were made, of which the most important are as follows:

- It is essential to understand resource capacity and to ensure that adequate funding is secured for staff. These platform and multi-arm trial designs probably save time and speed up getting answers but they still require similar amounts of resource per research question. The challenge for funders is to find a mechanism for funding and review of trial adaptations that facilitates delivery and minimises burden while also managing the risks involved.
- The biomarker testing process should be kept as simple as possible and for the UK, as much as possible within the NHS infrastructure.
- The trial needs to be informed by state-of-the-art preclinical evaluations in both disease subtype analysis and preclinical drug testing to maximise the quality of the applications to pharma for drug access.
- The setting needs to be positioned within the optimal phases of drug development with a clear line of sight to potential registration: FOCUS4 may have worked better as a Phase I/IIb platform trial.
- Platform trials need to be nimble and able to adapt quickly with emerging new biological discoveries. This is difficult in a sometimes turgid clinical trial regulatory framework.
- Finally, engagement, tenacity and enthusiasm are paramount from the chief investigator and trial management group. Without this, a trial of this complexity would fail.

Conclusions

FOCUS4 demonstrated the successful implementation of an adaptive stratified medicine trial, and fulfilled its objectives in that three stratified trials and one unstratified subgroup trial were activated, three of which reported a clear outcome. Adding molecular stratification to an adaptive multiarm study increases complexity and reduces the proportion of patients eligible for randomisation. FOCUS4-N showed that capecitabine monotherapy is an effective maintenance therapy for CRC. Adavosertib has significant activity notably in left-sided colorectal tumours with *TP53* and *RAS* mutation and warrants further investigation.

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Implications for health care

Oral capecitabine monotherapy is an effective maintenance treatment in terms on improving duration of disease control, but does not increase overall survival.

Future research implications

- Stratified medicine trials are feasible in solid tumours though significant challenges exist, particularly in establishing strong relationships with drug manufacturers to enable access to the relevant medicines.
- The *KRAS*/*TP53* double-mutant subgroup of CRC is associated with a poor prognosis and may have specific vulnerabilities to Wee1 inhibition.
- Wee1 inhibition has potential for treatment of mCRC, especially for patients with left-sided colon or rectal primaries, and warrants further evaluation.
- The window after 4 months of initial therapy provides a robust setting for evaluation of drug efficacy in CRC.
- Capecitabine is an appropriate control regimen for future maintenance therapy studies in mCRC.
- Stratified medicine studies are feasible in mCRC but require strong support from analyses supporting the proposed hypotheses, including data from preclinical testing platforms to provide the optimal justification for studies of this type.
- Strong relationships with pharma and a clear line of sight to registration are also critical to success.

Implications for decision-makers

Stratified medicine platform studies are feasible and may speed up research; however, the true costs of such complex adaptive studies are significant.

Trial registration

This trial is registered as ISRCTN90061546.

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