Capecitabine Versus Active Monitoring in Stable or Responding Metastatic Colorectal Cancer After 16 Weeks of First-Line Therapy

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Capecitabine Versus Active Monitoring in Stable or Responding Metastatic Colorectal Cancer After 16 Weeks of First-Line Therapy: Results of the Randomized FOCUS4-N Trial

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abstract

PURPOSE Despite extensive randomized evidence supporting the use of treatment breaks in metastatic colorectal cancer (mCRC), they are not universally offered to patients despite improvements in quality of life without detriment to overall survival (OS). FOCUS4-N was set up to explore the impact of oral maintenance therapy in patients who are responding to first-line therapy.

METHODS FOCUS4 was a molecularly stratified trial program that registered patients with newly diagnosed mCRC. The FOCUS4-N trial was offered to patients in whom a targeted subtrial was unavailable or biomarker tests failed. Patients were randomly assigned using a 1:1 ratio between maintenance capecitabine and active monitoring (AM). The primary outcome was progression-free survival (PFS) with secondary outcomes including OS toxicity and tolerability.

RESULTS Between March 2014 and March 2020, 254 patients were randomly assigned (127 to capecitabine and 127 to AM) across 88 UK sites. Baseline characteristics were balanced. There was strong evidence of efficacy for PFS (hazard ratio = 0.40; 95% CI, 0.21 to 0.75; $P < .0001$), but no significant improvement in OS (hazard ratio, 0.93; 95% CI, 0.69 to 1.27; $P = .66$) was observed. Compliance with treatment was good, and toxicity from capecitabine versus AM was as expected with grade ≥ 2 fatigue (25% *v* 12%), diarrhea (23% *v* 13%), and hand-foot syndrome (26% *v* 3%). Quality of life showed little difference between the groups.

CONCLUSION Despite strong evidence of disease control with maintenance therapy, OS remains unaffected and FOCUS4-N provides additional evidence to support the use of treatment breaks as safe management alternatives for patients who are stable or responding to first-line treatment for mCRC. Capecitabine without bevacizumab may be used to extend PFS in the interval after 16 weeks of first-line therapy.

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ASSOCIATED CONTENT

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Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Treatment breaks in patients receiving palliative chemotherapy for metastatic colorectal cancer (mCRC) reduce toxicity burden and improve quality of life (QoL).[1] However, current standards either mandate or recommend a strategy of continuing therapy, until progression or excess toxicity. Standard maintenance strategies in high-income countries favor combined oral capecitabine with intravenous bevacizumab once every 3 weeks,[2,3] on the basis of the phase III CAIRO3[4] and AIO-0207[5] studies. Health economic evaluation of this approach has previously indicated a lack of cost-effectiveness driven by nonsignificant improvement in overall survival (OS) and high costs of intravenous bevacizumab (drug plus administration).[6] Previous studies have evaluated a range of strategies to either completely stop therapy as a treatment holiday, reducing toxicities and hospital visits, or attenuate therapy, removing certain drugs as a maintenance therapy in comparison with historic standard-of-care continuation of maximum tolerated dose of treatment. Meta-analysis of these approaches overall shows no difference in OS.[7] Notably, maintenance strategies, almost uniformly, demonstrate an improvement in progression-free survival (PFS), but at the expense of ongoing (though attenuated) toxicity and unending multiple hospital visits for intravenous therapy. In the FOCUS4-N trial (embedded within the FOCUS4 trial

CONTEXT

Key Objective

In patients with metastatic colorectal cancer, first-line systemic anticancer therapy (SACT) with palliative intent aims to extend overall survival (OS) while maintaining quality of life. Current guidelines recommend a maintenance strategy of oral capecitabine and bevacizumab in patients with disease control after 4-6 months of induction SACT. This is based upon improved progression-free survival (without evidence of OS benefit) compared with a complete treatment break with active monitoring (AM). FOCUS4-N aims to establish the impact of maintenance capecitabine monotherapy versus AM.

Knowledge Generated

These results demonstrate that capecitabine can double the time until return to induction SACT. However, patients may adopt an AM approach without detriment in OS and with less toxicity.

Relevance

FOCUS4-N provides information for patients and clinicians, which will assist decision making at the end of induction SACT. Capecitabine without intravenous bevacizumab is likely more cost-effective than the current recommended approach of capecitabine and bevacizumab.

program, see the Data Supplement [online only]), we have explored the oral strategy of capecitabine only versus active monitoring (AM). This will allow us to study the potential impact on PFS, toxicity, and QoL, which will enable patients and clinicians to choose an optimum approach tailored to the individual.

The FOCUS4 trial program is a molecularly stratified umbrella platform trial (Data Supplement) that evaluated safety and efficacy of novel treatments in targeted biomarker subgroups within a phase II or III trial setting. The trial used adaptive statistical methodology that allowed the addition of new therapies and the dropping of ineffective ones and including a nonstratified comparison (FOCUS4-N) for patients in whom a molecularly stratified comparison was unavailable or the biomarker tests failed for their tumor tissue. In the Data Supplement, we describe the design and methods for patient registration and biomarker testing. In this article, we report the findings of FOCUS4-N, which tested the efficacy of capecitabine as a maintenance therapy versus AM in patients with mCRC.

METHODS

Trial Approvals, Patient Eligibility, and Recruitment

The trial and subsequent amendments were approved by the UK National Ethics Committee Oxford (reference 13/SC/0111) and by the relevant regulatory body MHRA (CTA# 20363/0400/001 and EudraCT# 2012-005111-12).

Patients age at least 18 years with newly diagnosed locally advanced or mCRC were eligible for registration in the FOCUS4 trial program (see the Data Supplement for details of FOCUS4 design and registration methods). Patients whose tumors had remained stable or responded to treatment according to their 16-week computed tomography (CT) were assessed for eligibility for the FOCUS4-N comparison. In addition to the registration eligibility criteria, patients were required to have a baseline randomly assigned CT scan performed within 4 weeks prerandomization; a minimum 3-week washout period between the last chemotherapy or biologic therapy dose and the first capecitabine dose; adequate renal (creatinine clearance $>$ 50 mL/min) and liver function; and a WHO performance status of 0-2. Patients who were eligible for either FOCUS4-N or a molecularly stratified trial were offered entry into either and given the option of which study to participate in, followed by appropriate consent.

In the first phase of FOCUS4 between January 2014 and June 2017, patients with raised baseline platelet count (thrombocytosis) were considered ineligible on the basis of previous data from the COIN trial (which indicated a significant survival detriment in this patient group receiving an intermittent strategy).[1] A subsequent individual patient data meta-analysis of phase II or III intermittent strategy trials did not confirm the observation from COIN.[8] Thus, between June 2017 and March 2020, eligibility criteria were adapted, allowing inclusion of this patient group with thrombocytosis.

Trial Procedures

Patients randomly assigned to capecitabine were asked to continue taking the drug until disease progression, death, or intolerable toxicity. Capecitabine was dosed according to standard guidelines, orally twice daily for 14 days followed by a 7-day rest period without capecitabine tablets.

Patient tumor status was assessed every 8 weeks by CT scan reviewed at the treating hospital site according to RECIST version 1.1.[9] Toxicities and symptoms were assessed locally every 4 weeks from random assignment or start of treatment using NCI CTCAE (version 3.0). Patients were followed until progressive disease, at which point the

patient was recommended to restart first-line systemic therapy.

Treatment was stopped for grade ≥ 3 toxic effects or persistent toxicities judged medically important or not tolerated by the patient, until the toxicity resolved to grade 1 or better. After stopping treatment, capecitabine could be reinitiated at a reduced dose. Any stoppage for ≥ 28 days was not permitted, with the patient discontinued from trial therapy but remaining under follow-up.

QoL data using EQ-5D were collected at random assignment, every 8 (7-9) weeks until progression, 4 weeks after end of trial treatment, 3 months after progression, and then every 6 months.

Statistical Methods

Treatment allocation. Patients were allocated to capecitabine or AM by a centrally managed telephone service at the MRC Clinical Trials Unit at University College London, using a 1:1 allocation ratio by minimization with a random element of 20%. Minimization factors were treating hospital site, primary tumor site (right colon, left colon, or rectum), WHO performance status (0, 1, or 2), 16-week CT scan result (stable disease and partial or complete response), number of metastatic sites (none, one, or two or more), and first-line therapy regimen (fluorouracil, capecitabine, or neither; both oxaliplatin and irinotecan, irinotecan only, or neither; and cetuximab or panitumumab, bevacizumab, or no monoclonal antibody).

Outcome measures. The primary FOCUS4-N outcome was PFS, defined as time from random assignment to either disease progression (according to RECIST criteria) or death from any cause. Patients without a PFS event were censored at the time of their last recorded CT scan. OS was a secondary outcome, defined as time from random assignment to death from any cause with patients censored at last recorded disease assessment, blood measurement, or anticancer treatment. Other secondary outcomes included safety, toxicity, QoL, and tumor response. QoL was analyzed using mixed-effects linear modeling with patient-level random intercepts and time slopes, with differences by the treatment arm tested by evaluating the area under the curve from the model.

Sample size calculation. The FOCUS4-N target sample size was calculated using the Analysis of Resources for Trials program implemented in Stata software. Given that the recruitment rate into FOCUS4-N was dependent on the availability of other molecular comparisons, failure of biomarker testing, or patient choice, exact recruitment figures were unknown at the trial commencement. Various scenarios were used to estimate the recruitment rate over 5 years, and we assumed a 4-month median PFS in the AM arm (on the basis of COIN trial data). A total of 644 patients (635 events) would provide 80% power of detecting a hazard ratio (HR) of 0.8 at the two-sided 5% significance level.

In March 2020, the COVID-19 pandemic resulted in temporary closure of FOCUS4 to new recruitment. Following Independent Data Monitoring Committee review and recommendation, a decision was taken to close recruitment permanently in April 2020 as trial funding was nearing its end. A previous review of the implications of reduced recruitment on the statistical power of FOCUS4-N had been considered by our funders who recommended that, despite reduced power, the trial should close in 2020 and report the data accrued up to that point. Furthermore, at analysis, it became clear that the observed HR was substantially more extreme than the target HR on which we based our original sample size.

Statistical analysis. All analyses were performed according to a predefined statistical analysis plan agreed before database lock. We analyzed using Stata statistical software, version 16.1 (Stata Corporation, TX). The primary analysis was performed according to intention-to-treat with a secondary per-protocol analysis defined by patients who completed at least one cycle of trial treatment (≥ 28 days). Patients were censored according to the following criteria. For survival status, we censored patients on the date that they were last known to be alive, either via collection of prescription from their hospital pharmacy or attendance at a follow-up visit or CT scan. For PFS, we censored patients without progression on the date of the last CT scan showing no progression. For patients who died before any follow-up visit or CT scan, we used the date of death as the date of the event and assumed death without progression, provided that the death occurred within 3 months of random assignment or any previous scan confirming no progression.

Kaplan-Meier curves were used to present survival data and Cox regression modeling to estimate HRs between randomized groups. Unadjusted HRs and the ones adjusted for the stratification factors used to minimize patients into allocated groups (primary analysis) were estimated. A further analysis also adjusted for resection status, timing of metastatic disease, alkaline phosphatase, white blood cell count, age of tumor sample, and use of aspirin at baseline. Deviation from nonproportional hazards was assessed using regression of scaled Schoenfeld residuals against the log of time.

RESULTS

Recruitment and Compliance

Across 88 UK hospitals, between January 2014 and March 2020, 1,434 patients were registered into FOCUS4, of whom 924 underwent successful biomarker assessment and completed 16 weeks of first-line therapy with either stable or responding disease (Data Supplement). Of these patients, 254 were randomly assigned to FOCUS4-N (Fig 1), 127 to AM and 127 to maintenance capecitabine.

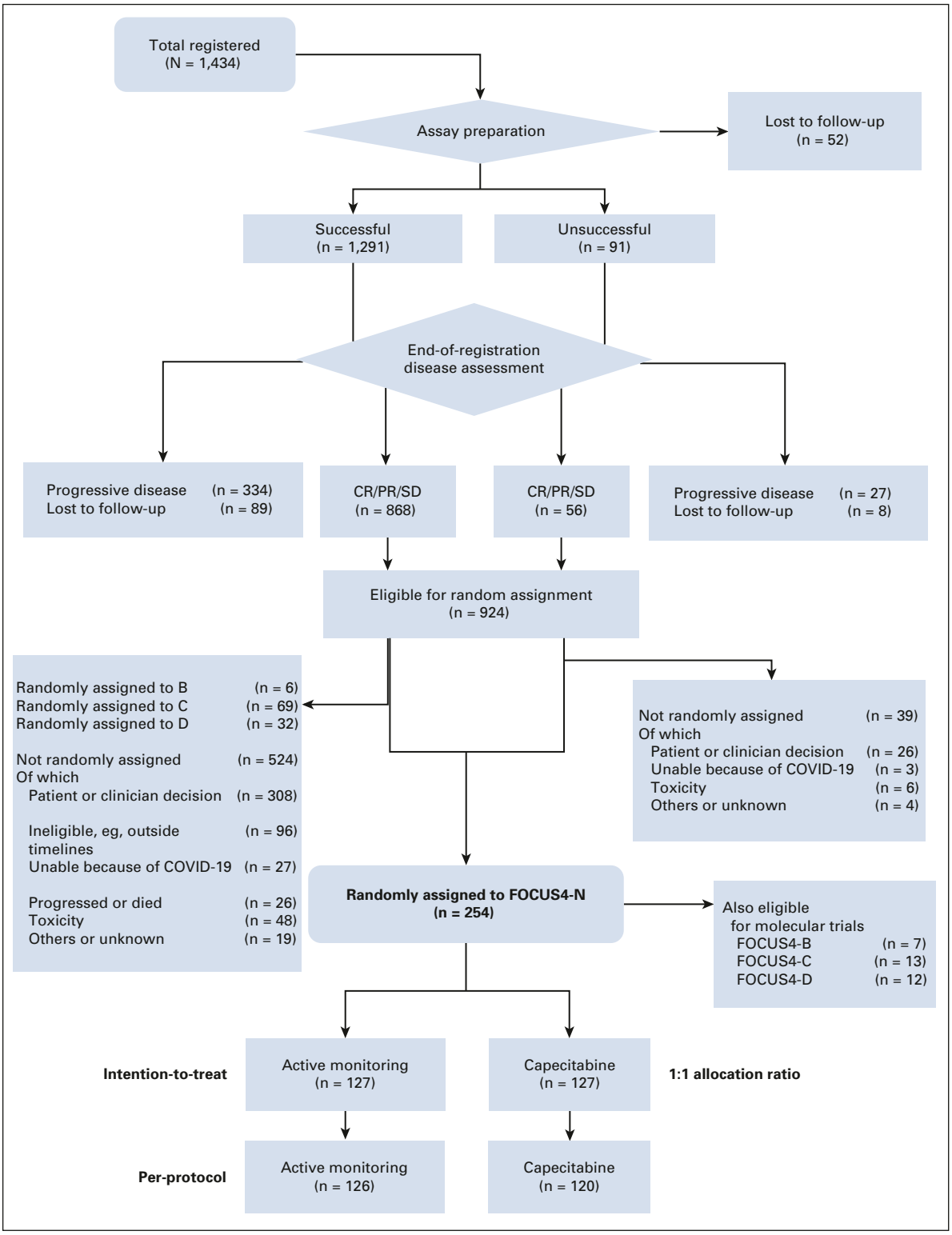

FIG 1. Flow diagram showing patient flow through the FOCUS4-N trial. CR, complete response; PR, partial response; SD, stable disease.

Baseline demographic and clinical characteristics were well-balanced between the study arms (Table 1 and Appendix Table A1, online only). Most patients had widespread synchronous metastatic disease with about half having an unresected primary tumor. A right-sided primary tumor location was present in about one third. The majority were treated with doublet chemotherapy (irinotecan-based 57%) without a monoclonal antibody (as bevacizumab is not reimbursed in the United Kingdom). The Data Supplement shows induction chemotherapy for all patients

TABLE 1. Baseline Characteristics for FOCUS4-N

Characteristic	Active Monitoring (n = 127)	Capecitabine (n = 127)
Mean (SD) age, years	63.7 (10.9)	64.7 (9.6)
Sex, No. (%)		
Male	76 (60)	86 (68)
Female	51 (40)	41 (32)
Baseline WHO performance status, No. (%)		
0	76 (60)	80 (63)
1	49 (39)	45 (35)
2	2 (2)	2 (2)
Site of primary tumor, No. (%)		
Right colon	45 (35)	47 (37)
Left colon	32 (25)	33 (26)
Rectum	50 (39)	47 (37)
Current state of primary tumor, No. (%)		
Resected primary	62 (49)	54 (43)
Unresected primary	61 (48)	68 (54)
Unresected local recurrence	4 (3)	5 (4)
No. of metastatic sites, No. (%)		
No metastases	2 (2)	4 (3)
One	41 (32)	40 (31)
Two or more	84 (66)	83 (65)
Timing of metastases, No. (%)		
Metachronous	40 (31)	21 (17)
Synchronous	85 (67)	101 (80)
No metastases	2 (2)	4 (3)
Missing data	0 (0)	1 (1)
Disease assessment at end of first-line treatment, No. (%)		
Complete response	3 (2)	5 (4)
Partial response	75 (59)	71 (56)
Stable disease	49 (39)	51 (40)
Fluoropyrimidine drug used during first-line treatment, No. (%)		
FU	95 (75)	97 (76)
Capecitabine	32 (25)	30 (24)
Oxaliplatin or irinotecan used during first-line treatment, No. (%)		
Both oxaliplatin and irinotecan	2 (2)	2 (2)
Oxaliplatin only	50 (39)	50 (39)
Irinotecan only	73 (57)	71 (56)
Neither	2 (2)	4 (3)
Monoclonal antibody used during first-line treatment, No. (%)		
Cetuximab/panitumumab	25 (20)	20 (16)
Bevacizumab	6 (5)	7 (6)
No antibody	96 (76)	100 (79)
PIK3CA mutation status, No. (%)		
Mutation	15 (12)	14 (11)
Wild type	96 (76)	100 (79)
Failed	7 (6)	5 (4)
Insufficient tumor	9 (7)	8 (6)
BRAF mutation status, No. (%)		
Mutation	13 (10)	17 (13)
Wild type	103 (81)	98 (77)
Failed	2 (2)	4 (3)
Insufficient tumor	9 (7)	8 (6)
RAS mutation status, No. (%)		
Mutation	68 (54)	68 (54)
Wild type	47 (37)	48 (38)
Failed	3 (2)	3 (2)
Insufficient tumor	9 (7)	8 (6)
TP53 mutation status, No. (%)		
Mutation	61 (48)	62 (49)
Wild type	33 (26)	28 (22)
Failed	3 (2)	2 (2)
Could not be tested	18 (14)	24 (19)
Insufficient tumor	12 (9)	11 (9)
MSI status, No. (%)		
MSS	108 (85)	104 (82)
MSI	2 (2)	3 (2)
Failed	2 (2)	4 (3)
Could not be tested	6 (5)	8 (6)
Insufficient tumor	9 (7)	8 (6)
Total	127 (100)	127 (100)

Abbreviations: FU, fluorouracil; MSI, microsatellite instable; MSS, microsatellite stable; SD, standard deviation.

in FOCUS4, and the Data Supplement shows disease response to induction chemotherapy on the basis of biomarker subgroup. The molecular characteristics are shown in Table 1 (and the Data Supplement for all FOCUS4 participants), showing that only 37% had an *RAS* wild-type tumor reflecting NHS England policy of not allowing treatment breaks for patients on epidermal growth factor receptor monoclonal antibodies.

Compliance with randomized allocation was good with only one patient in the AM arm receiving capecitabine approximately 6 months before progression. Patients in

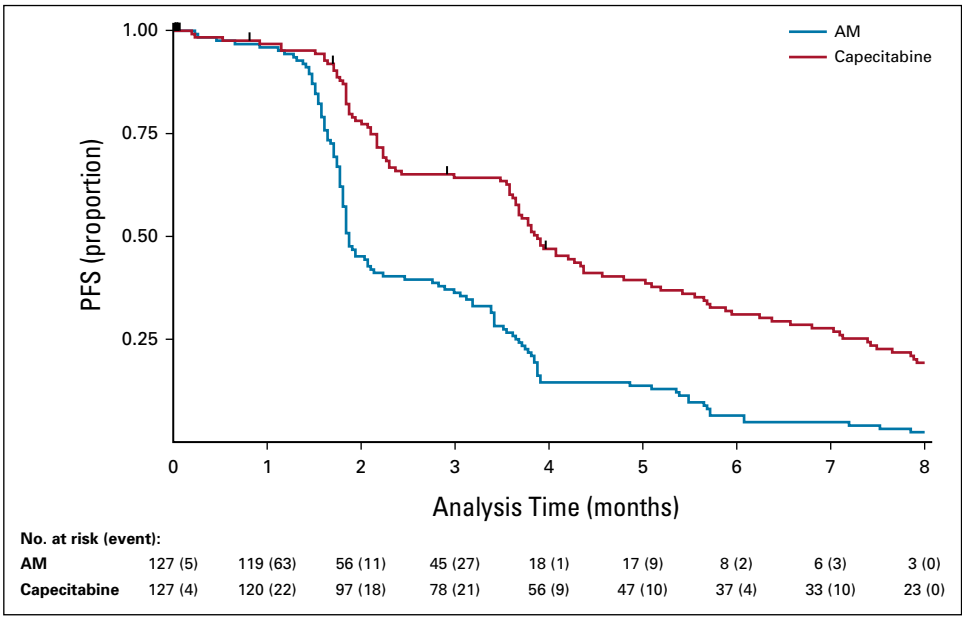

FIG 2. Kaplan-Meier curve for PFS in FOCUS4-N. Cox regression HR, adjusted for minimization factors = 0.40 (95% CI, 0.21 to 0.75), $P < .0001$. Minimization factors: location of primary tumor (left, right, and rectum), baseline WHO performance status, baseline disease assessment, No. of metastases, first-line therapy (fluoropyrimidine, oxaliplatin or irinotecan, and monoclonal antibody), and biomarker cohort, stratified for FOCUS4 trial timepoints. AM, active monitoring; HR, hazard ratio; PFS, progression-free survival.

the capecitabine arm received a median of four cycles (interquartile range, 2-8).

Primary Outcome: PFS

There were 122 of 127 PFS events in the AM arm and 117 of 127 in the capecitabine arm. The median PFS in the capecitabine arm was 3.88 months (95% CI, 3.65 to 4.37) and 1.87 months (95% CI, 1.81 to 2.14) in the AM arm. Unadjusted and adjusted HRs were 0.44 (95% CI, 0.33 to 0.57), $P < .0001$ and 0.40 (95% CI, 0.21 to 0.75), $P < .0001$, respectively. Figure 2 shows Kaplan-Meier curves. Per-protocol analyses demonstrated very similar findings; unadjusted and adjusted HRs were 0.42 (95% CI, 0.32 to 0.55), $P < .0001$ and 0.38 (95% CI, 0.28 to 0.51), $P < .0001$, respectively. There was no evidence to suggest deviation from the proportional hazards assumption ($P = .084$).

OS

There were 90 of 127 deaths in the AM arm and 99 of 127 deaths in the capecitabine arm. The median time to death was 15.2 months (95% CI, 12.1 to 18.5) in the AM arm versus 14.8 months (95% CI, 23.7 to 18.6) in the capecitabine arm, with no survival difference between the arms; unadjusted and adjusted HRs were 1.00 (95% CI, 0.75 to 1.33), $P = .98$ and 0.93 (95% CI, 0.69 to 1.27), $P = .66$, respectively. Kaplan-Meier curves are presented in Figure 3. There was no evidence to suggest deviation from the proportional hazards assumption ($P = .58$).

Subgroup Analyses

Preplanned subgroup analysis for PFS (Fig 4A) suggested better PFS with a maintenance strategy in left-sided tumors (HR 0.38 *v* 0.56 for right-sided, interaction $P = .13$), and a similar observation was seen with OS (HR 0.82 for left-sided *v* 1.37 for right-sided, interaction $P = .076$; Fig 4B). There was a suggestion that patients with tumoral loss of phosphatase and tensin homolog and *PIK3CA* mutations may show less benefit from maintenance capecitabine than other molecular subgroups (PFS HR 0.74, OS HR 1.47), although this was not statistically significant. For OS, the only other notable subgroup effect was that those with stable disease at random assignment appeared to benefit from maintenance capecitabine, whereas those with partial response did not (OS HR 0.63 and 1.42, respectively, interaction $P = .005$; Fig 4B). Swimmer plots show the distribution of individual patient PFS duration and timing of CT scans by left- versus right-sided disease (Appendix Fig A1, online only).

Toxicity

Cumulative toxicities were substantially less in the AM arm, with increased toxicities associated with capecitabine maintenance including diarrhea, dry skin, fatigue, nausea, and palmar-plantar erythema (PPE; Fig 5). Ideally, a maintenance therapy should result in no toxicity. Incidence of grade zero as the worst toxicity reported per patient is therefore instructive and is as follows for AM and capecitabine maintenance, respectively: nausea 74% versus

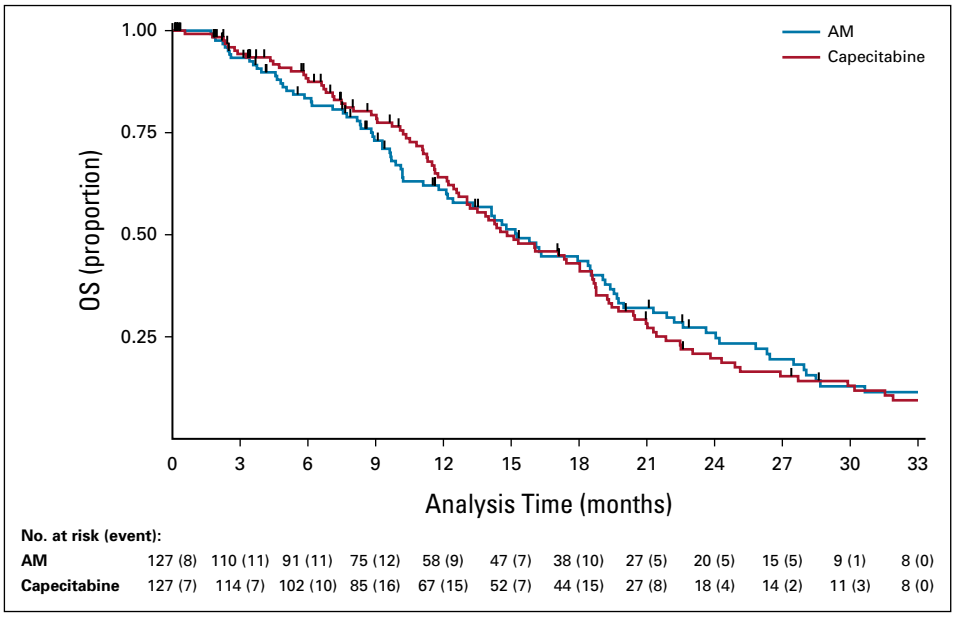

FIG 3. Kaplan-Meier curve for OS in FOCUS4-N. Cox regression HR, adjusted for minimization factors = 0.93 (95% CI, 0.69 to 1.27), $P = .66$. Minimization factors: location of primary tumor (left, right, and rectum); baseline WHO performance status; baseline disease assessment; No. of metastases; first-line therapy (fluoropyrimidine, oxaliplatin or irinotecan, and monoclonal antibody); and biomarker cohort, stratified for FOCUS4 trial timepoints. AM, active monitoring; HR, hazard ratio; OS, overall survival.

67%, diarrhea 72% versus 46%, stomatitis 90% versus 77%, dry skin 83% versus 77%, PPE 87% versus 44%, and anemia 69% versus 54% (Appendix Table A2, online only).

During the trial, 51% of patients who received capecitabine had at least one cycle delayed, 37% had a dose reduction, and 34% missed at least one dose (within a cycle). Fifty percent of capecitabine patients commenced at least four cycles, and 25% commenced at least eight cycles.

QoL

EQ-5D forms were completed in 93% (AM) and 90% (capecitabine) at baseline (prerandomization but post-induction chemotherapy). The Protocol (online only) mandated completion every 8 weeks until progression and 6-monthly thereafter; for analysis purposes, all available forms were forced into an 8-week schedule. On this basis, 63%, 45%, and 33% of randomly assigned patients had data available at 8, 16, and 24 weeks, respectively, with continuous decline thereafter. Modeling was applied to data up to 48 weeks, since data became too sparse beyond this. No notable differences were seen in mobility, self-care, usual activities, anxiety, and depression. There was a suggestion that pain and discomfort might have been experienced less within the capecitabine maintenance arm ($P = .11$, Fig 6). This may be due to symptoms associated with increased rates of progression in the AM arm.

DISCUSSION

Choices on how to proceed with palliative treatment, in the large majority of patients with incurable mCRC, with stable or responding disease after 16 weeks of first-line therapy need careful consideration with the patient at the core. Discussions must be informed by the impact of receiving systemic anticancer therapy over the preceding period. This should include evaluation of the burden of toxicity and QoL, as well as the response to treatment. Pooled data from key phase II and III trials suggest minimal impact on OS from a maintenance or continuation strategy but do show the ability to delay a return to full combination therapy by implementation of a maintenance therapy. Notably, the FOCUS4-N data support the use of an oral only therapy (capecitabine) to extend PFS and delay a return to combination therapy by an average of two months. There is a clear cost to the patient for this improved PFS seen with maintenance capecitabine including worse toxicity in terms of diarrhea, fatigue, nausea, skin rash, and PPE albeit mostly at grade ≤ 2, and these factors should be used to further inform decision making. There was no difference in QoL scores between the two arms. It is notable that the swimmer plots (Appendix Fig A1) suggest that about a third of patients experience an extended PFS beyond 16 weeks with maintenance capecitabine, suggesting significant fluoropyrimidine sensitivity, while a third of patients demonstrate relative insensitivity to fluoropyrimidine monotherapy and may indicate a further need to explore

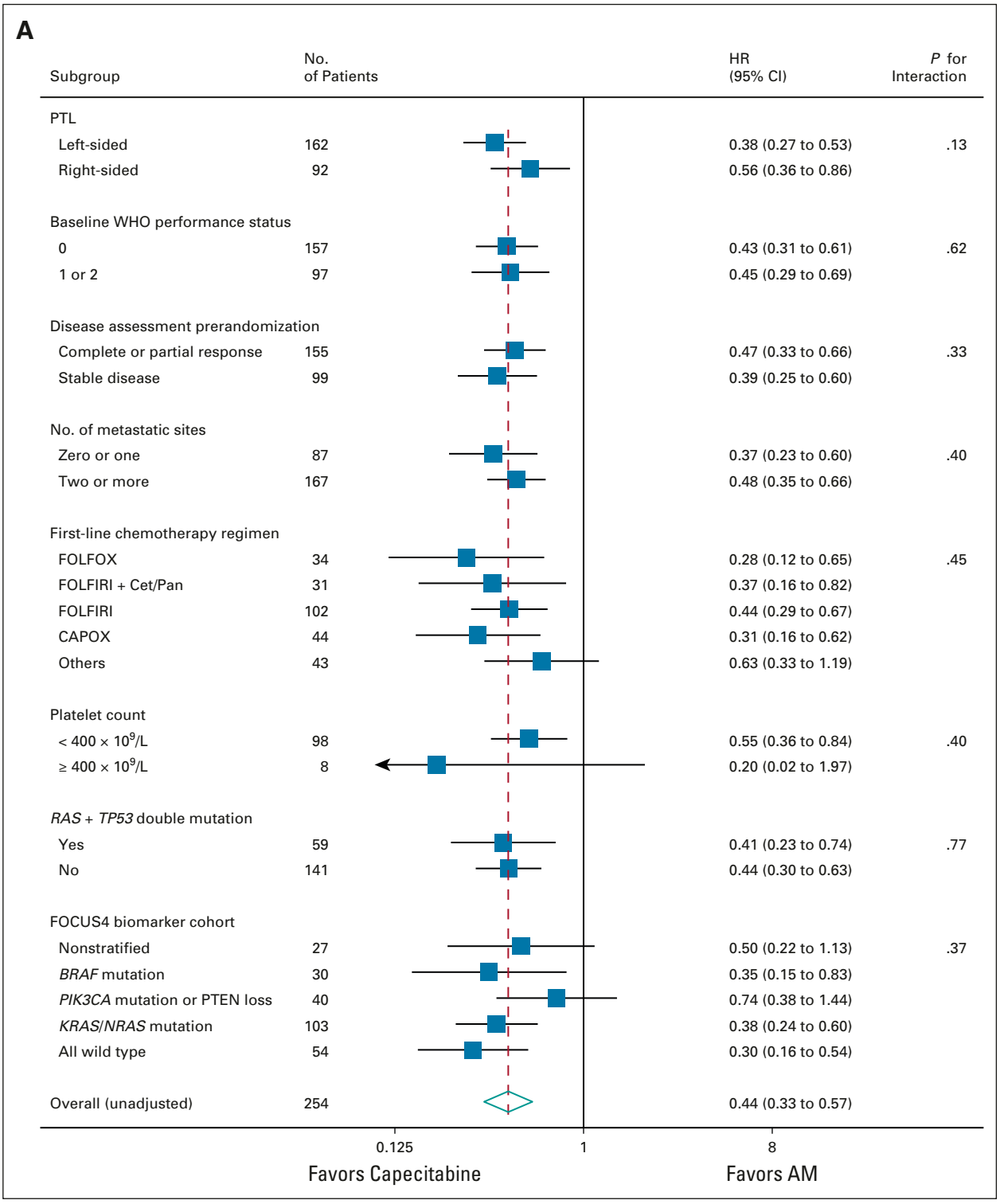

FIG 4. (A) Forest plot of subgroup analyses for PFS (unadjusted HRs). (B) Forest plot of subgroup analyses for OS (unadjusted HRs). AM, active monitoring; CAPOX, capeciteabine with oxaliplatin; Cet, cetuximab; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; OS, overall survival; Pan, panitumumab; PFS, progression-free survival; PTEN, phosphatase and tensin homolog; PTL, primary tumor location. (continued on next page)

predictive biomarkers of efficacy for this strategy. Preplanned subgroup analysis suggests that patients with stable disease at the end of 16-week induction period may gain a significant survival benefit from maintenance capecitabine, but this is not corroborated in other studies where the same phenomenon was assessed.[8]

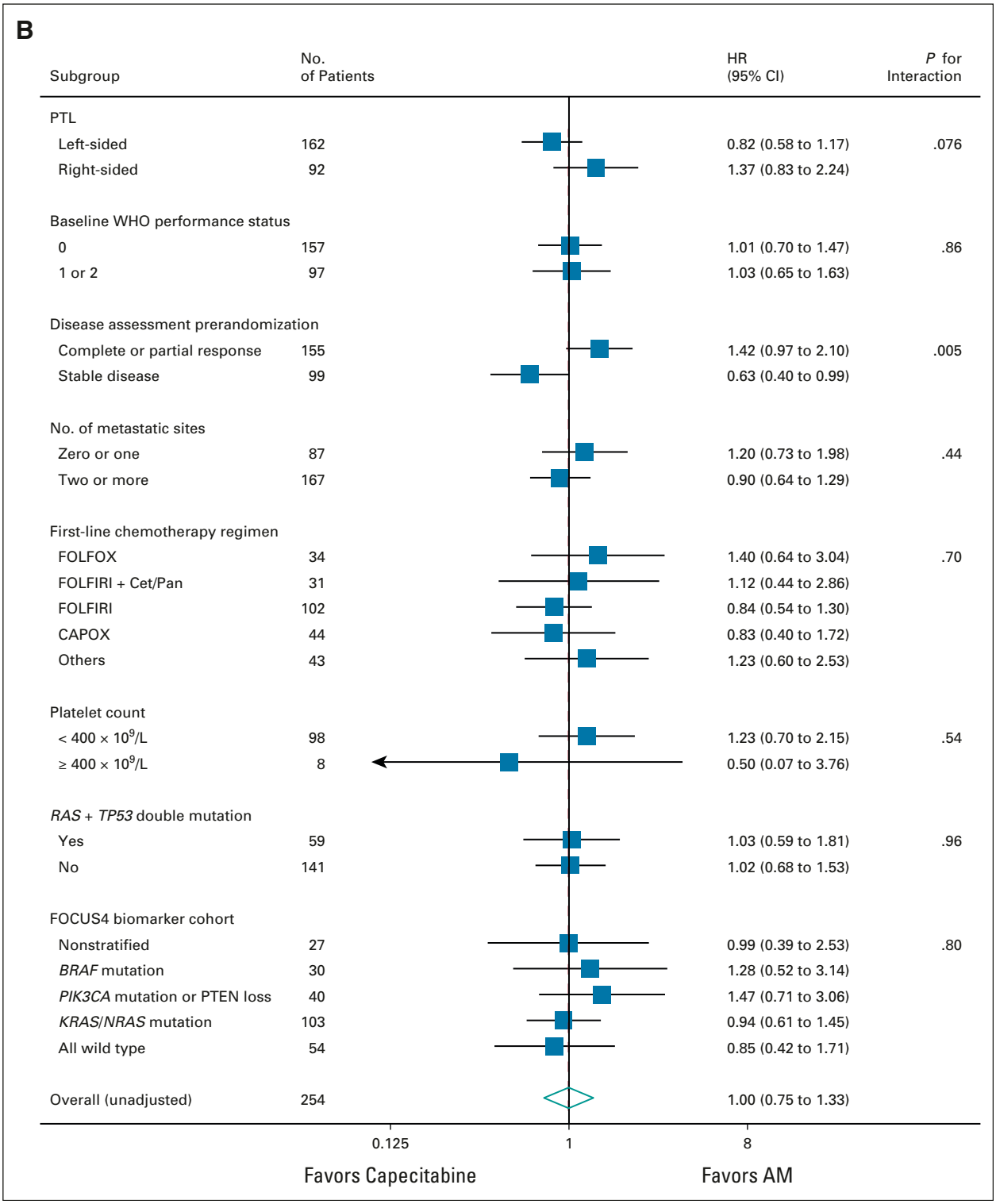

FIG 4. (Continued).

Although this trial is underpowered to evaluate OS, it demonstrates very similar median values of 14.8 versus 15.2 months between the two arms with an HR of 0.93 (P = .66) when adjusted for minimization factors. It is informative to compare these data with those of CAIRO3, which compared an AM strategy with capecitabine plus

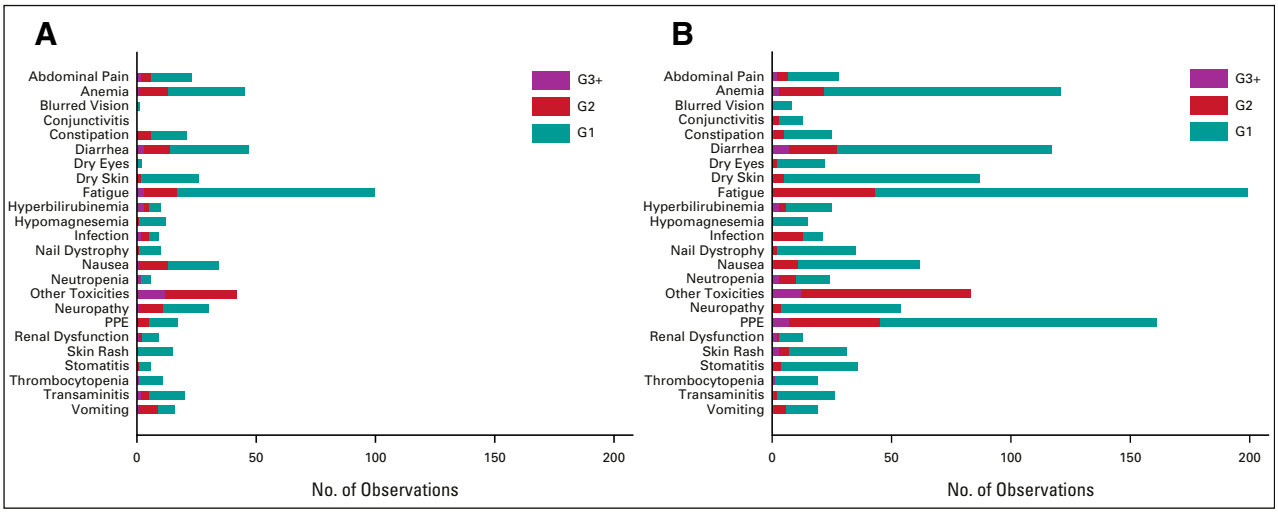

FIG 5. Cumulative reported toxicity by randomized group: (A) active monitoring (n = 127) and (B) capecitabine (n = 127). G, grade; PPE, palmar-plantar erythema.

bevacizumab maintenance with comparable effects on PFS (HR = 0.40, $P < .0001$; cfFOCUS4-N adjusted HR = 0.40, $P < .0001$) and nonsignificant OS effect (HR = 0.83, $P = .06$).[4] Cross-trial comparisons carry notable caveats and must be undertaken with caution as CAIRO3 included patients with better prognosis than FOCUS4-N and both their median PFS and cycle number on maintenance therapy were approximately double those of ours. However, it does suggest that the main driver of PFS improvement when using capecitabine plus bevacizumab is the capecitabine. Individual patient data meta-analysis has also shown no OS benefit from current maintenance therapy strategies.[8]

On the basis of a subgroup analysis from the much larger phase III COIN study,[1] which demonstrated a survival detriment in patients with a baseline thrombocytosis receiving a complete treatment break (HR = 1.55; $P = .0018$), we elected not to recruit patients with baseline thrombocytosis to the FOCUS4 trial program from January 2014 to June 2017. Wishing to validate or refute this finding, we undertook an individual patient data meta-analysis to assess thrombocytosis as a predictive marker of the benefits or otherwise of an intermittent or continuous therapy strategy.[8] This evaluation did not validate our COIN finding on thrombocytosis, and thus, trial eligibility was adapted to allow these patients to enroll. Within FOCUS4-N overall, 3% (n = 8) of patients had baseline thrombocytosis, and thus, our study is underpowered to explore this predictive phenomenon further. Because of our conservative approach, FOCUS4-N under-represents approximately 25% of patients with mCRC who typically have thrombocytosis at baseline, a known worse prognosis group. However, given our findings in the individual patient data meta-analysis, we do not feel that this undermines our more general conclusions, which are independent of baseline platelet count.

Owing to funding restrictions in the UK National Health Service, bevacizumab is not routinely available for patients with mCRC, and in patients with *RAS* wild-type tumors, epidermal growth factor receptor monoclonal antibodies are only available in the first-line setting, with restrictions in England preventing treatment interruption of cetuximab/panitumumab for longer than 6 weeks. Additionally, during the FOCUS4-D trial recruitment period,[10] patients with *RAS* wild-type and *BRAF* wild-type tumors were eligible for random assignment and were preferentially recruited into that trial. These factors make for a selective group of patients recruited to FOCUS4-N during that time. From a molecular perspective, 59% of patients randomly assigned in the FOCUS4-N trial had an *RAS* mutation and 15% a *BRAF* mutation. Reassuringly, the Forest plots (Figs 4A and 4B) do not show any significant differences in PFS or OS on the basis of these molecular criteria.

In conclusion, despite strong evidence of disease control with maintenance therapy, OS remains unaffected and FOCUS4-N provides additional evidence to support the use of treatment breaks as safe management alternatives for patients entering treatment de-escalation after 16 weeks of induction therapy for mCRC. If maintenance therapy is selected following consideration of the advantages and disadvantages in consultation with a particular patient, capecitabine without bevacizumab may be used to extend PFS, in the interval after doublet or triplet therapy, essentially doubling the period before recommencing full-dose induction therapy. Notably, these data also provide tools to best inform the dialogue between patients and clinicians on the pros and cons of the different approaches and their trade-offs.

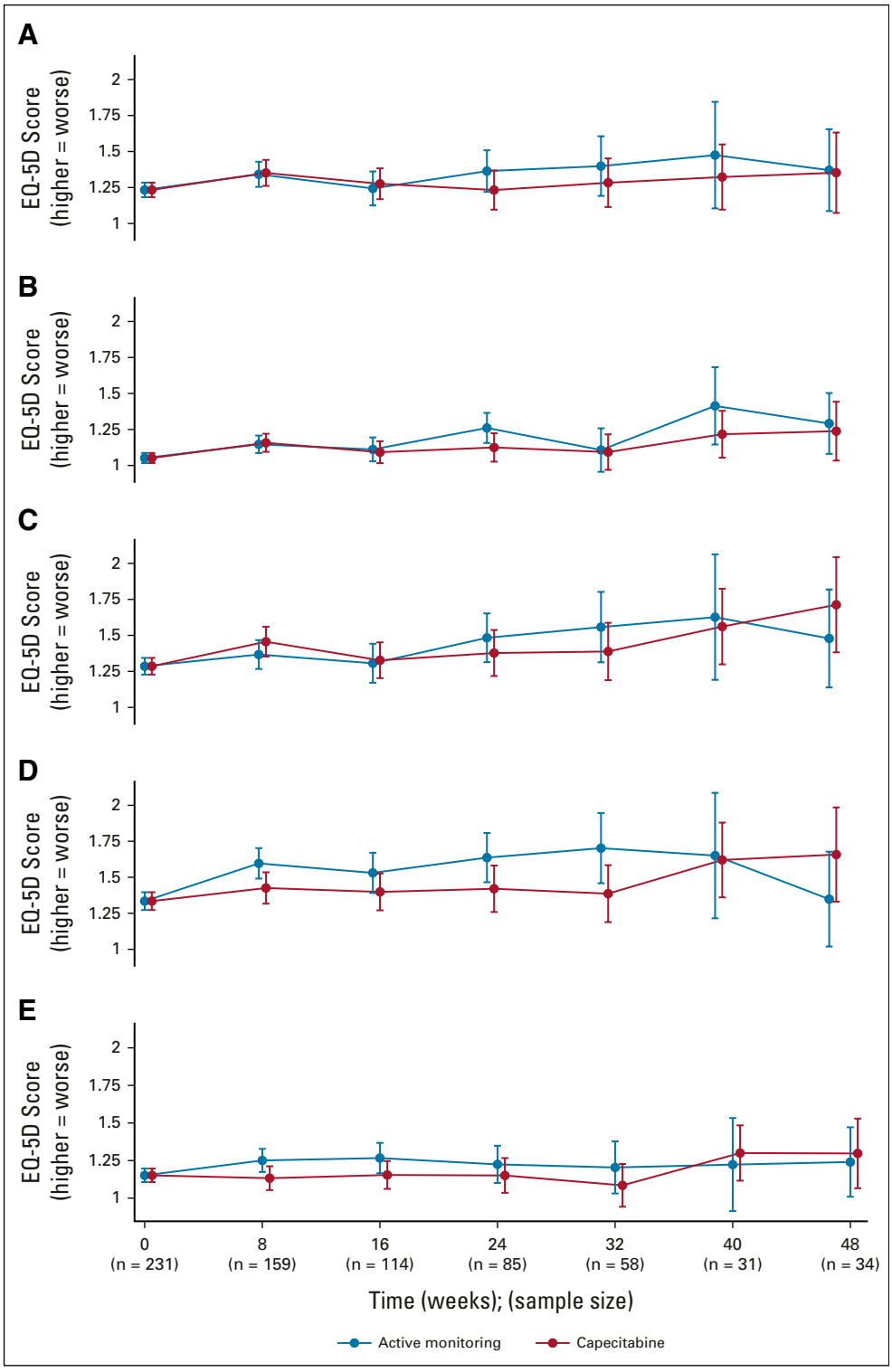

FIG 6. Quality of life measured by EQ-5D by randomized group: (A) mobility: X^2 for AUC difference = 0.86(1), P = .35; (B) self-care: X^2 for AUC difference = 1.64(1), P = .20; (C) usual activities: X^2 for AUC difference = 0.06(1), P = .81; (D) pain and discomfort: X^2 for AUC difference = 2.49(1), P = .11; and (E) anxiety and depression: X^2 for AUC difference = 1.03(1), P = .31; AUC, area under the curve.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Individual deidentified participant data (including data dictionaries) can be shared upon appropriate application to the MRC CTU at any time from full publication. Study protocols and statistical analysis plan have been provided in the Data Supplement with this manuscript. Going forward, it is proposed that data will be shared with an appropriate international collaborative repository to enable future IPD meta-analysis.

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ACKNOWLEDGMENT

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Capecitabine Versus Active Monitoring in Stable or Responding Metastatic Colorectal Cancer After 16 Weeks of First-Line Therapy: Results of the Randomized FOCUS4-N Trial

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	Ilyas	Ali
	Nawa	Amin
	Gareth	Barker
	Michelle	Chen
	Sarah	Chilcott-Burns
	James	Clark
	Susan	Cleator
	Christopher	Coyle
	Andrea	Davis-Cook
	Keyury	Desai
	Matthew	Flook
	Victoria	Harding
	Gillian	Hornzee
	Victoria	Latham
	Luzviminda	Llemit Ramos
	Charles	Lowdell
	Maria	Martinez
	Daniel	Meredith
	Laura	Morland
	Annette	Musallam
	Chynna	Pascual
	Emily	Pickford
	David	Pinato
	Keira	Pudge
	Ramya	Ramaswami
	Azeem	Saleem
	Amalia	Saucan

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Sarah	Stimpson
	Regina	Storch
	Caroline	Ward
	Adrian	Zebrowski
Huddersfield Royal Infirmary	Jo	Dent (PI)
	Zenab	Ahmed
	Mohammad Irfan	Alam
	Nick	Brown
	Sam	Dale
	Nicky	Daker
	Denise	Hancock
	James	Harris
	Lisa	Horner
	Ibrar	Hussain
	Jeremy	Hyde
	Paula	Gomes
	Rebecca	Jenkins
	Christopher	Knight
	Adam	Mawer
	Mandy	Madigan
	Belinda	McLean
	Sabiha	Ravat
	Hannah	Riley
	Jodie	Rowan
	Simone Deborah	Ryan
	Lisa	Shaw
	Selina	Shaw
	Kathryn	Smith
	Christine	Turner
	Georgina	Turner
	Hayley	Webster
	Tracy	Wood
Northampton General Hospital	Roshan	Agarwal (PI)
	Sabri	Ahmed
	Caroline	Duncombe
	Tasnim	Ebrahimjee
	Rachel	Gabitass
	Ethelwolda	Goyena
	Andrea	Hillyer
	Jane	Hosea

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Mohammad	Hussain
	Kashif	Jarral
	Andrea	Jones
	Andrea	Kempa
	Adnan	Masood
	Craig	Macmillan
	James	Maloy
	Katherine	McGrath
	Jan	Miles
	Onyinye	Ndefo
	Paula	O'Connell
	Malgorzata	Polnik
	Ehsan	Rahman
	Shahriar Mohammed	Reza
	Sharon	Ryan
	Simon	Stapley
	Elizabeth	Tee
	Lenka	Zvirinska
Pinderfields Hospital	Iva	Damyanova (PI)
	Ashraf	Alkhaldi (PI)
	Gireesh	Kumaran (PI)
	Usman	Ahmad
	Aneeka Shubnum	Altaf
	Julie	Ball
	Louise	Benton
	Kevin	Birbeck
	Lynsey	Bourner
	Richard	Bowers
	Hollie	Brooke
	Ellis	Burton
	Julie	Burton
	Deborah	Cooper
	Elizabeth	Clayton
	Jane	Eastwood
	Aimee	Fletcher
	Rebecca	Foster
	Darren	Gomersall
	Hassan	Hameed
	Aimee	Hayton-Bott
	Charlotte	Hirst
	Claire	Hutsby

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Andrew M	Jackson
	Annette	Jones
	Konstantinos-Vellios	Kamposioras
	Patricia	Kane
	Tracey	Lowry
	Stephanie	Lupton
	Joanna	Lyle
	Kate	Norton
	Ganesh	Radhakrishna
	Vishal	Ramdhani
	Muhammad Bilal	Razzaq
	Ayesha	Sheikh
	Hira	Yousif
Beatson West of Scotland Cancer Centre	Janet	Graham (PI)
	Tareq	Abdullah
	Ghada	Al-Salih
	Martin	Ball
	Karen	Bell
	Anette	Charlick
	Maureen	Connolly
	Jill	Dempster
	Alan	Foulis
	Paula	Henry-Stephenson
	Jill	Graham
	Lesley	Hickey
	Sandra	Jenkins
	Sai Juan	Jia
	Jennifer	Keith
	Donna	Kelly
	Audrey	Leonard
	Gail	Lynch
	Alex	McDonald
	Jordan	McGill
	Anne	McKillop
	Austin	McInnes
	Fiona	McQueen
	Nazia	Mohammed
	Paul	Mooney
	Maria	Nygren
	Shilpa	Thapar

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Kirsty	Ross
	Patricia	Roxburgh
	Pavlina	Spiliopoulou
	Eileen	Soulis
	Kirsteen	Stuart
	Rasheed	Syed
	Ashita	Waterston
	Cheryl	Wilson
Ysbyty Gwynedd	Catherine	Bale (PI)
	Kelly	Andrews
	Naomi	Boyle
	Claire	Fuller
	John	Grant
	Emma	Hall
	Anna	Mullard
	Wendy	Saxton
	Nick	Stuart
	Alice	Thomas
	Linzi	Williams
	Rachel	Williams
Withybush General Hospital	Sarah	Gwynne (PI)
	Maung	Moe (PI)
	Fawwaz	Arikat
	Denisa	Asandei
	Sandra	Evans
	Eirianydd	Garrard
	Sophie	Glynn-Williams
	Colette	Griffiths
	Rachel	Hughes
	Catherine	MacPhee
	John	Murphy
	Kirsty	Pope
	Rocio	Riba
	Sally-Ann	Rolls
	Abigail	Taylor
	Carol	Thomas
	Helen	Thomas
	Vallipuram	Vigneswaran
Aberdeen Royal Infirmary	Leslie	Samuel (PI)
	Fay	Annison
	Sharon	Armstrong

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Abimbola	Barango
	Balazs	Binnyei
	Gillian	Brand
	Kay	Campbell
	Angie	Cheyne
	Michael	Christie
	Kathryn	Connolly
	Pat	Cooper
	Amber	Johnson
	Susan	Martin
	Celia	Meneses
	Graeme	Murray
	Nicola	Price
	Sue	Rodwell
	Mhairi	Scott
	Margaret	Smith
	Bartosz	Was
	Mehmood	Zaidi
	Ishtiaq	Zubairi
Cheltenham General Hospital	Kim	Benstead (PI)
	Jaqueline	Aberdeen
	Rehana	Bakawala
	Sarah	Beazer
	Colin	Binks
	Lucy	Blake
	Bethan	Cartwright
	Samuel	Croly
	Lin	Crossley
	Rachel	Durrant
	David	Farrugia
	Janet	Forkes
	Emma	Gilbert
	Fabrizio	Mauri
	Elaine	Pratten
	Elisabeth	Read
	Nick	Reed
	Rachel	Sayers
	Neil	Shepherd
	Stephen	Shepherd
	Jennifer	Smith
	Sarah	Stanley

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Catherine	Stuart-Grumbar
	Bilal	Topia
	Kate	Trigg-Hogarth
Clatterbridge Centre for Oncology	Nasim	Ali (PI)
	Wesley	Artist
	Shaker	Abdallah
	Alexandra	Bailey
	Danielle	Campbell
	Maggie	Cantrell
	Joanne	Cliff (nee Mooney)
	Thomas	Davies
	Helen	Flint
	Amy	Ford
	Barbara	King
	Ayman	Madi
	Samah	Massalha
	Laura	McAllister
	Amir	Montazeri
	Joanne	Mullen
	Julie	O'Hagan
	Anna	Olsson-Brown
	Katharine	Pelton
	Kelly	Richardson
	Sandra	Robinson
	Joseph	Sacco
	Sarah	Stuart
	Hollie	Wilson
	Pembe	Yesildag
	Mariah	Zavery
Royal Devon and Exeter Hospital	Melanie	Osborne (PI)
	Kizzy	Baines
	Tamika	Chapter
	Elizabeth	Davey
	Susan	Downer
	Dawn	Edwards
	Theresa	Lawless
	James	Leavy
	Mark	Napier
	Emma	Robjohns
	Patrick	Sarsfield
	Ingrid	Seath

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Shirley	Todd
	Jane	Thompson
	Fiona	Walters (nee Hall)
	Claire	Webb
	Julia	Weston
Southampton General Hospital	Tim	Iveson (PI)
	Liane	Armstrong
	Andrew	Bateman
	Adrian	Bateman
	Emma	Brown
	Holly	Burton
	Tracey	Callen
	Bethany	Caruana
	Caroline	Chau
	Tracey	Day
	Efe	Evbuomwan
	Meg	Gale
	Julie	Gwilt
	Sara	Hosseini-Moein
	Alice	Johnson
	Leah	Long
	Steve	McKenzie
	Charlotte	Rees
	Rasha	Said
University College Hospital	John	Bridgewater (PI)
	Adrienne	Abioye
	Mahfuja	Ahmed
	Shamima	Akther
	Maise	Al Bakir
	Adelaide	Austin
	Holly	Baker
	Jaytee	Barnett
	Nina	Bason
	Isabelle	Brown
	Alexa	Childs
	Louise	Coyle
	Patricia	Danaswamy
	Kanishka	Dissansayke
	Rosina	Donovan
	Lola	Enemuwe
	Victor	Eneh

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Gabrielle	Gould
	Todd	Gumbleton
	Selina	Gurung
	Gemma	Hector
	Sonya	Hessey
	Daniel	Hochhauser
	Sabrina	Holohan
	Michelle	Hung
	Georgios	Imseeh
	Adoracion	Jayme
	Sarah	Kerr
	Khurum	Khan
	Jennifer	Laude
	Xiao	Lu
	Gina	Margai
	Katie	Matthews
	Eman	Mohamad
	Fatima	Mohamed
	Sam	Morris
	Anna	Nikopoulou
	Mayur	Patel
	Maria	Power
	Prakash	Rao
	Manuel	Rodriguez-Justo
	Derya	Sahin
	Kai Keen	Shiu
	Luke Owen	Steventon
	Mark	Sunga
	Hinesh	Tailor
	Anisa	Tariq
	Varji	Thayalan
	Jennifer	Thomas
	Christopher	Wanstall
	Kristian	Warnes
	Christopher	Whitton
	Georgina	Wood
Monklands Hospital	Lisa	Rogers (PI)
	Anne	McKillop (PI)
	Ashita	Waterston (PI)
	Paula	Botham
	June	Carr
	Louise	Devlin

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Katie	Douglas
	Grainne	Dunn
	Mohammed	El-Abdullah
	Lynn	Glass
	Kirsteen	Hamill
	Susan	Hastings
	Rebecca	Heron
	Chloe	MacDonald
	Steven	Marshall
	Laura	Miller
	Geradline	O'Dowd
	Aqilah	Othman
	Diana	Park
	Angela	Scullion
	Denise	Vigni
	Kai	Yahya
Charing Cross Hospital	Harpreet	Wasan (PI)
	Thalia	Afxentiou
	Riz	Ahmed
	Melloney	Allnutt
	Gareth	Barker
	Abigail	Caldow
	Jolene	Carioni
	Sarah	Chilcott-Burns
	Andrea	Davis-Cook
	Yomi	Fatola
	Chee	Goh
	Dorothy	Gujral
	Gillian	Hornzee
	Eleni	Josephides
	Charlotte	Kelly
	Daleep	Kumar
	Priya	Limbu
	Luzviminda	Llemit Ramos
	Charles	Lowdell
	Sophia	Magwaro
	Rochelle	McIntyre
	Philippa	Nutkins
	Shola	Ogegbo
	Anna	Osei-Kofi
	Susan	Ramsey
	Pippa	Riddle

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Amalia	Saucan
	Helen	Saxby
	Chantelle	Simpson
	Aspa	Spyrou
	Kirsty	Tunna
	Iman	Yahya
	Adrian	Zebrowski
Churchill Hospital, Oxford	Tim	Maughan (PI)
	David	Badcock
	Magdalena	Benysek
	Rosita	Broderick
	Anne	Butterfield
	Evelyn	Chan
	Philip	Charlton
	David	Church
	Richard	Cousins
	Louise	Cowen
	Joanne	Davies
	Steven	Davis
	Alfonso	Gonzalez Blas
	Will	Goodman
	Nikki	Hayward
	Clare	Jacobs
	Patrycja	Jastrzebska
	Evanthia	Komninidou
	Jonathan	Lau
	Carolina	Lepiato
	Clare	Marken
	Kerrie	Marston
	Mark	Middleton
	Ann	Murphy
	Rebecca	Muirhead
	Adrian	Nicholson
	Robin	Peach-Toon
	Navin	Pol
	Sally	Rich
	Nicola	Stoner
	James	Wakelin
	Lai Mun	Wang
	Andrew	Weaver
	Sandie	Wellman

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Anthony	Wilson
	Rebecca	Wiltshire
	Martha	Woodward
	Kirsten	Wynn
Leicester Royal Infirmary	Anne	Thomas (PI)
	Will	Steward (PI)
	Elizabeth	Andrzejewski
	Tracey	Alexander
	Sarah	Attridge
	Julie	Barlow
	Theresa	Beaver
	Amy	Branson
	Meera	Chauhan
	Aurora	Del Pozo
	Hadia	Haque
	Hannah	Holdsworth
	Rahima	Ibrahim
	Chinenye	Iwuji
	Mohammed	Karolia
	Lydianne	Lock
	Mohammed	Mahgoub
	Adrian	Nicholson
	Ahmed	Osman
	Katherine	Perkins
	Sarah	Porter
	Thiaghrajon	Sridhar
	Judith	Underwood
	Balaji	Varadhan
	Julia	Walker
	Kevin	West
	Joanna	Wood
Raigmore Hospital	Walter	Mmeka (PI)
	Anglise	Addison
	Seonaid	Arnott
	Karen	Callum
	Denise	Campbell
	Fiona	Campbell
	Kay	Kelly
	Alison	Macdonald
	Angela	Macgregor
	Carol	Macgregor

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Zoe	Maciver
	Laura	Maclennan
	Jude	Madeleine
	Melanie	McIlroy
	Mary	McKenzie
	Neil	McPhail
	Alison	Nicholls
	Marion	Paterson
	Leslie	Samuel
	Georgina	Simpson
	Glenda	Sinclair
	Feng Yi	Soh
	Grant	Stenhouse
	Joan	Stewart
	Una	Taylor
	Zoe	Urquhart
Victoria Hospital (Kirkcaldy)	Sally	Clive (PI)
	Brian	Adamson
	Julie	Aitken
	John	Brush
	Rebecca	Cain
	Lesley	Cargill
	Shona	Cheyne
	Clare	Cliff
	Hazel	Cree
	Karen	Gray
	Sophie	Iwanikiw
	Fiona	Johnston
	Alastair	Matthews
	Wendy	McCorry
	Catriona	Mclean
	Fiona	Murdoch
	Ibrahim	Nawroz
	Julie	Penman
	Anna	Scott
	Maria	Simpson
	Deepak	Subedi
	Jennifer	Tait
	Michelle	Tingley
	Linzi	Wilson
Princess Alexandra Hospital (Harlow)	John	Bridgewater (PI)

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Gemma	Cook
	Amelia	Daniel
	Venkatesh	Gajapathy
	Evelyn	Holmes
	Tayo	Jaiyesimi
	Joanne	Kellaway
	Teresa	Light
	Lucinda	Melcher
	Cait	Rees
	Vasi	Sundaresan
Royal Surrey County Hospital	Tony	Dhillon (PI)
	Mazhar	Ajaz
	Nawa	Amin
	Humyraa	Aziz
	Izhar	Bagwan
	Catherine	Blake
	Fiona	Butler
	Penny	Champion
	Karen	Chan
	Sebastian	Cummins
	Tineke	Edmunds
	Sharadah	Essapen
	Andrew	Furness
	Laura	Gordon
	Di	Grainger
	Helen	Graves
	Imogen	Heenan
	Kirsty	Horwood
	Daniel	Jennings
	Natasha	Kamboh
	Aga	Kehinde
	Karla	Lee
	Sibylle	Lintott
	Gaybrielle	Livingstone
	Cheryl	Marriott
	Catherine	Medcalf
	Aruna	Medisetti
	Mahomed	Moosa
	Gayathri	Nagarajan
	Sarah	Oakes
	Sue	Sargent

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Alexandra	Stewart
	Hasina	Thandar
	Claire	Thompson
	Katharine	Webb
	Rosalyne	Westley
	Julia	Whittle
	Julie	Wilkinson
	Rebecca	Wills
St Helens Hospital	Zahed	Khan (PI)
	Rachel	Cassidy
	Jenny	Cotton
	Lisa	Dobson
	Nicola	Hornby
	Sheila	Kelly
	Amanda	McCairn
	Jeanette	Ribton
	Michelle	Robinson
	Carol	Ross
	Victoria	Thomas
Chesterfield Royal Hospital	Vanessa	Wilshaw (PI)
	Ibrahim	Al-Modaris
	Rebecca	Clark
	Aurora	Del Pozo
	Alice	Dewdney
	Nicky	Ford
	Rachel	Gascoyne
	Neeta	Gogna
	Charlotte	Hoult
	Emma	Hudson
	Kelly	Pritchard
	Martin	Shepherd
	Lesley	Stevenson
	Danesh	Taraporewalla
	Julie	Toms
	Katie	Wallace
	Julie	Whitehead
	Lucinda	Wilson
Ipswich Hospital	Gopalakrishnan	Srinivasan (PI)
	Zoltan	Szucs (PI)
	Deborah	Abrams
	Debbie	Austin

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Carlos	Gonzalez
	Matthew	Howlett
	Natalie	Lloyd
	Rita	Ng
	Paul	Ridley
	Kirubah	Selvaraj
	Liz	Sherwin
	Bamini	Sivarajah
	Susan	Upson
	Angharad	Williams
	Jason	Wong
Royal Hampshire County Hospital	Luke	Nolan (PI)
	Louise	Beattie
	Julie	Conti
	Duncan	Cooke
	Victoria	Corner
	Adrienn	Fazekasne Fulep
	Angela	Frith
	Julie	Gwilt
	Samantha	Hammond
	Liz	Happle
	Lesley	Hollister
	Roger	Hudson
	Abigail	Hughes
	Lauriane	Kerwood
	Matthew	Pitt
	Balvinder	Shoker
	Rao	Vuyyuru
Peterborough City Hospital	Catherine	Jephcott (PI)
	Terri-Anne	Baker
	Helen	Bowyer
	Kerrie	Cavanagh
	Rebecca	Chilvers
	Marilyna	Chong
	Laura	Costello
	Abigail	Hollingdale
	Steph	Lawrence
	Heather	Maccoll
	Carla	Martino
	Claire	Palombo
	Stuart	Richmond

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Richard	Skells
	Laura	Simon
	Claire	Snowden
	Lisa	Wilde
	Louise	Wilmer
Calderdale Royal Hospital	Jo	Dent (PI)
	Mohammad Irfan	Alam
	Nick	Brown
	Nicky	Daker
	Sam	Dale
	Denise	Hancock
	James	Harris
	Lisa	Horner
	Jeremy	Hyde
	Rebecca	Jenkins
	Christopher	Knight
	Mandy	Madigan
	Adam	Mawer
	Belinda	McLean
	Sabiha	Ravat
	Hannah	Riley
	Jodie	Rowan
	Simone Deborah	Ryan
	Lisa	Shaw
	Selina	Shaw
	Kathryn	Smith
	Christine	Turner
	Georgina	Turner
	Hayley	Webster
	Tracy	Wood
Derriford Hospital	David	Sherriff (PI)
	Rebecca	Aaron
	Bridget	Aire
	Baffour	Amo-Takyi
	Erin	Brennan
	Lucy	Cadmore
	Leonie	Eastlake
	Laura	Evenden
	Kay	Facey
	Olivia	Fraser
	Julie	Froud

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Bojidar	Goranov
	Irene	Harvey
	Maggie	Kalita
	Sarah	Kingdon
	Mike	Marner
	Laura	Marks
	Susan	McFarlane
	Chelsea	Morton
	Anna	Mucha
	Sarah	Prance
	Olivia	Reed-Poysden
	Peter	Sankey
	Helen	Smith
Macclesfield District General Hospital	Victoria	Lavin (PI)
	Ganesh	Radhakrishna (PI)
	Catherine	McBain (PI)
	Victoria	Adinkra
	Dane	Bradwell
	Lisa	Brookes
	Helen	Burns
	Nicola	Dawson
	Catherine	Fenson
	Lisa	Hardstaff
	Abbi	Henderson
	Christy	Henderson
	Pippa	Hill
	Debra	Jowle
	Mark	Lawrence
	Joanna	Longden
	Nicola	Lunt
	Marilyn	McCurrie
	Karen	Rotchell
	Barbara	Townley
	Helen	Wassall
	Julie	Whitehead
	Lesley	Wilkinson
	Iain	Woodhouse
Torbay District General Hospital	Nangi	Lo (PI)
	Michele	Allison
	Kenneth	Almedilla
	Emmie	Arbury

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Lauren	Blunt
	Jo	Blurton
	Catherine	Brookman
	Ian	Buley
	Shelley	Chamberlain
	Stacey	Davies
	Angela	Foulds
	Meadow	Fisher-Crisp
	Joanne	Garfield-Smith
	Petra	Gee
	Caera	Good
	Hannah	Griffin
	Andrew	Harford-Brown
	Prithvi	Jampana
	Ingrid	Koehler
	Tyler	Lowe
	Sally	Maddison
	Mitchell	McMillan
	Louise	Medley
	Lyn	Micklewright
	Louise	Paatz
	Maeve	Pomeroy
	Helen	Randall
	Fleur	Rogers
	Lorraine	Thornton
	Christine	Tsang
	Elaine	Vandecandalaere
	Sarah	Wright
Addenbrooke's Hospital	Hugo	Ford (PI)
	Athar	Ahmad
	Alexandra	Azevedo
	Lesley	Bennett
	Elizabeth	Blake
	Mark	Bolton
	Rebecca	Bradley
	Jane	Bushen
	Joanna	Calder
	Anita	Chhabra
	Kathy	Chin
	Sarah	Clark
	Joseph	Gallagher

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Svitlana	Iyevkova
	Rashmi	Jadon
	Catherine	Jephcott
	Natalie	Jones
	Hannah	Loveday
	Jane	Macdonald
	Betania	Mahler-Araujo
	Debra	Mansergh
	Ultan	McDermott
	Lindsay	Piper
	Amy	Strong
	Catherine	Thorbinson
	Saji	Victor
	Naval	Vyse
	Amanda	Walker
	Emma	Wong
	Zsuzsa	Zaborszky
Guy's Hospital (London)	Paul	Ross (PI)
	Samantha	Barrett
	Eva	Batovska
	Jessica	Brady
	Maribel	Boyce
	Laura	Camburn
	Lorna	Caplis
	Noan Minh	Chall
	Jason	Chow
	Chi Yee	Chung
	Sophie	Clark
	Sarah	Cleary
	Victoria	Donovan
	Sandra	Esteban Moreno
	Adrienn	Fazekasne Fulep
	Lucy	Featherstone
	Michael	Flanagan
	Laura	Green
	Sara	Hulf
	Arun	Karnad
	Sara	Kazemzadeh
	Vevangaune	Ketjiperue
	Choi Chin	Lau
	Nick	Maisey

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Simranjit	Mehta
	Ngozi	Muoneke
	Theodorah	Nago
	Rita	Njoku
	Vitalis	Nwokorie
	Temi	Olusi
	Kishen	Patel
	Amy	Quinn
	Catherine	Rogers
	Hannah	Rush
	Susie	Slater
	Anita	Soma
	Chara	Stavraka
	Harriet	Waine
	Sally	Walker
St George's Hospital (London)	Fiona	Lofts (PI)
	Doraid	Alrifa
	Nia	Alsamarrai
	Jason	Chow
	Alice	Dainty
	Lorette	Ffolkes
	Caroline	Finlayson
	Claire	Gilmartin
	Anne	Haldeos
	Sam	Hollingworth
	Geoffrey	Howell
	Robert	Ingham
	Kay	Laurent
	Vitalis	Nwokorie
	Antonio	Pesino
	Mark	Quarrell
	Agne	Sekmokaite
	Jesusa	Toledo
Wrexham Maelor Hospital	Simon	Gollins (PI)
	Stacy	Ackerley
	Ashraf	Alkhaldi
	Kelly	Andrews
	Rachel	Davies
	Alistair	Ellis-Jones
	Emma	Hall
	Rachel	Hughes

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Ravi	Kodavatiganti
	Arwel	Lloyd
	Bethan Wyn	Owen
	Beryl	Roberts
	Charley-Anne	Rutter
	Jane	Stockport
	Gemma	Szabo
	Ian	Walker
	Claire	Watkins
	Glesni	Williams
	Linzi	Williams
Glan Clwyd Hospital	Simon	Gollins (PI)
	Elizabeth	Allan
	Jill	Andrews
	Kelly	Andrews
	Lisa	Ashley
	Llinos	Davies
	Rachel	Davies
	Clair	Domeney
	Sarah	Evans
	Emma	Hall
	Jane	Heron
	Ravi	Kodavatiganti
	Joanne	Lewis
	Arwel	Lloyd
	Carey	Macdonald-Smith
	Claire	McGregor
	Bethan Wyn	Owen
	Tracy	Parry-Jones
	Fiona	Redmond
	Beryl	Roberts
	Charley-Anne	Rutter
	Libby	Thackray
	Ian	Walker
	Jill	Westlake-Guy
	Linzi	Williams
	Stephanie	Wynne
James Cook University Hospital	Nick	Wadd (PI)
	Andrea	Boyce
	Alison	Chilvers
	Anthony	Donnelly

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Helen	Dunn
	Vicky	Hanlon
	Charlotte	Jacobs
	Steven	Liggett
	Craig	Mower
	Lisa	Peacock
	Jacqueline	Richards
	Agnieszka	Skotnicka
	Danielle	Sweeney
	Jane	Thompson
	Hans	Van der Voet
	Gill	Wheater
	David	Wilson
	Jason	Wong
Poole Hospital	Amelie	Harle (PI)
	Tamas	Hickish (PI)
	Michael	Adrio
	Maria	Alban
	Julian	Alexander
	Lyn	Allen
	Mary	Apps
	Beth	Aubrey
	Helen	Bradley
	Savina	Elitova
	Daniel	Fielding
	Maxine	Flubacher
	Deborah	Forster
	Melanie	Foster
	Louise	Heckford
	Jill	Hobson
	Hannah	James
	Min Yee	Lee
	Helen	Morling
	Victoria	Osborne
	Sharon	Power
	Victoria	True
	Craig	Vincent
	Roger	Wheelwright
Royal Cornwall Hospital	Richard	Ellis (PI)
	Linda	Allsop
	Nicholas	Ashley
	Kerry	Atkinson

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Nigel	Bailey
	Thea	Barlow
	Kayleigh	Bennett
	Carolyn	Brode
	Thomas	Cornell
	Alexander	Dengler
	Emma	Duley
	Sophia	Eloi
	Caroline	Goddard
	Aaron	Gould
	Anne	Griffiths
	Karina	Harris
	Peter	Helliwell
	Claire	Hill
	Louise	Johns
	Tinnaya	King
	Samantha	Lomax
	Kirsty	Maclean
	John	Madine
	Joe	Mathew
	John	McGrane
	Fiona	Minear
	Sharon	Moore
	Anna	Oakes
	Caroline	Parnell
	Kerena	Partridge
	Sallyanne	Platt
	Kirsty	Prout
	William	Pynsent
	Rebecca	Rogers
	Jenifer	Row
	Laura	Royle
	Johanna	Skewes
	David	Smith
	Darren	Snell
	Luke	Townley
Royal Free Hospital	Daniel	Krell (PI)
	Astrid	Mayer (PI)
	Tahmin	Ahmed
	Ian	Clark
	Jen	Fraser-Fish
	Roopinder	Gillmore

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Sara	Hamilton
	Ben	Marks
	Leah	Meaden
	Aarti	Nandani
	Tesha	Suddason
	Sharon	Thompson
	Elizabeth	Woodford
South Tyneside District Hospital	Ashraf	Azzabi (PI)
	Amy	Burns
	Kumud	Jain
	Judith	Moore
	Ruth	Tindle
St Bartholomew's Hospital (London)	David	Propper (PI)
	Waheeda	Abida
	Hayley	Blackgrove
	Joanne	Chin-Aleong
	Nikolaos	Diamantis
	Resmi	Jayachandran
	Sumaiya	Kamora
	Cheryl	Lawrence
	Alia	Mahboob
	Juan	Navarro
	Tanjil	Nawaz
	Pratistha	Panday
	Hannah	Payne
	Stephen	Russell
	Sarah	Slater
Yeovil District Hospital	Andrew	Allison (PI)
	Erica	Beaumont (PI)
	Matthew	Sephton (PI)
	Joanna	Allison
	Zenaida	Armstrong
	Claire	Barron
	Nigel	Beer
	Kate	Beesley
	Edwin	Cooper
	Sarah	De Bruijn
	David	Donaldson
	Tracey	Duckett
	Adam	Edwards
	Shirley	Fox

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Karen	Flynn
	Michelle	Kotze
	Michaela	Nock
	Jess	Perry
	Lucy	Pippard
	Kerry	Rennie
	Amber	Rowsell
	Rufus	Smith
	Lesley	Thomas
	Barbara	Williams-Yesson
Lincoln County Hospital	Zuzana	Stokes (PI)
	Antoinette	Adu
	Suzanne	Archer
	Sarah	Bell
	Jayne	Borley
	Sarah	Coombs
	Olesya	Francis
	Annette	Hilldrith
	Kathryn	Hoare
	Carol	Lockwood
	Maryanne	Okubanjo
	Rhiannan	Pegg
	Manuel	Ruiz-Echarri
	Thomas	Sheehan
	Anuradha	Sheth
	Andrew	Sloan
	Caroline	Taylor
	Ruth	Thoy
	Alyson	Wilson
Maidstone Hospital	Mark	Hill (PI)
	Doraid	Alrifa
	Elizabeth	Angus
	Paulette	Basham
	Lisa	Brown
	Tracey	Chambers
	Alison	Davison
	Jackie	Evans
	Sanjina	Kathuria
	Samantha	Kestenbaum
	Tiana	Kordbacheh
	Satish	Kumar
	Barbara	LeBrocq

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Gemma	McCormick
	Christos	Mikropoulos
	Ian	Pamphlett
	Joanne	Patterson
	Caroline	Rodger
	Holly	Slater
	Charlotte	Stevens
	Jeff	Summers
	Alicia	Synowiec
	Katy	Taylor
	Lisa	Tribe
Nottingham University Hospitals	Cristina	Lopez Escola (PI)
	Rebecca	Ashton
	Suha	Atabani
	Alex	Blades
	Emma	Blades
	Lauren	Blackburn
	Pauline	Brookes
	Eliot	Chadwick
	Caroline	Coulson
	Michelle	Cunnell
	James	Donworth
	Jade	Eggleton
	Susan	Elliott
	Joanne	Hobbs
	Shaymaa	Hosni
	Laura	Kirk
	Emma	Marshall
	Balwir	Matharoo-Ball
	Kayleigh	Mills
	Jamie	Mills
	Jeanette	Mulhurn
	Karen	Newcombe
	Vanessa	Potter
	Tin	Sang-Tsang
	Rosalind	Roberts
	Maria	Scott
	Rafael	Silverman
	Ananth	Sivanandan
	Tania	Slater
	Anita	Stevenson

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Richard	Swinden
	Jackie	Worville
	Georgina	Walker
	Andrew	Wright
Hinchingbrooke Hospital	Cheryl	Palmer (PI)
	Shilamba	Bramham
	Sue	Donnelly
	Simon	Duke
	Vanessa	Goss
	Beverley	Haynes
	Rebecca	Lam
	Elizabeth	Lee
	Sarah	Littlechild
	Adam	McGeoch
	Suzanne	Miller
	Agnieska	Osmanska
North Middlesex Hospital	John	Bridgewater (PI)
	Ernesto	Balaguer-Ruiz
	Girish	Bhome
	Moira	Durdy
	Lorraine	Hurl
	Shardul	Kulkarni
	Simranjit Kaur	Mehta
	Lucinda	Melcher
	Julia	Rees
	Jamila	Roehrig
	Rahi	Shah
	Chloe	Van Someren
Queen Alexandra Hospital	Ann	O'Callaghan (PI)
	Oluwatobi	Adeagbo
	Suhail	Baluch
	Kathy	Blight
	Sherilee	Cook
	Heather	Cuell
	Tracey	Dobson
	Mya	Gyi
	Antony	Higginson
	Samuel Luke	Hill
	Chloe	Holden
	Tracey	Lee

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Jayne	McCartney
	Badrriyya	Mohamedali
	Sethupathi	Muthuramalingam
	Andras	Nagy
	Eleanor	Taylor
	Mary	Wands
	Robert	Williams
	Carole	Wragg
Weston General Hospital	Stephen	Falk (PI)
	Paola	Di Nardo (PI)
	Marjorie	Tomlinson
	Kathy	Beard
	Sandra	Beech
	Hannah	Berry
	Debbie	Coles
	Donna	Cotterill
	Harvey	Dymond
	Symeon	Eleftheriadis
	Rajesh	Gamare
	Christine	Graham
	Serena	Hilman
	Sarah	Kidd
	Denise	Leighton-Price
	Hugh	Lloyd-Jones
	Andrew	McKendrick
	Kathryn	Munday
	Vivienne	Pixton
	Glenn	Saunders
	Ed	Sheffield
	Dawn	Simmons
	Axel	Walther
	Rachel	Warinton
	Tom	Wells
Glangwili General	Mau-Don	Phan (PI)
	Samantha	Coetzee
	Sonya	Goriah
	Praba	Gupta
	Ann	Hewins
	John	Murphy
	Zohra	Omar
	Bryan	Phillips

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Meena	Raj
	Kelly	Reed
	Rocio	Riba
Royal Albert Edward Infirmary	Francisca Marti	Marti (PI)
	Elena	Takeuchi (PI)
	Jennifer	Cannon
	Kate	Chilman
	Shien	Chow
	Louise	Devereaux
	Alison	Doran
	Diane	Forrest
	Karen	Moss
	Monica	Patel
	Angela	Power
	Wendy	Stevens
Sunderland Royal Hospital	Ashraf	Azzabi (PI)
	Hayley	Anderson
	Rod	Beard
	Jane	Cole
	Michelle	Edwards
	Adam	Hassani
	James	Henry
	Vivienne	Hullock
	Stephen	Laybourne
	Paula	Newton
	Rachel	Pearson
	Ian	Pedley
	Ian	Pepley
	Melanie	Robertson
	Fiona	Wakinshaw
	Kathryn	Wright
Basingstoke and North Hampshire Hospital	Charlotte	Rees (PI)
	Louise	Beattie
	Victoria	Corner
	Abigail	Edwards
	Adrienn	Fazekasne Fulep
	Angela	Frith
	Julie	Gwilt
	Liz	Happle
	Roger	Hudson

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Andrew	Jackson
	Lauriane	Kernwood
	Lauriane	Kerwood
	Kathryn	Leach
	Emma	Magras
	Asmat	Mustajab
	Christina	Narh
	Pennie	Porter
	Arun	Selvaraju
	Jackie	Smith
	Claire	Williams
Forth Valley Royal Hospital	Dawn	Storey (PI)
	Joanne	Blackburn
	Stephanie	Brogan
	Raj	Burgul
	Eilidh	Henderson
	Jane	Keddie
	Linnet	McGeever
	Kaye	McIlvar
	David	McIntosh
	Caroline	Mcleary
	Lynn	Prentice
	Annette	Riley
	Joanne	Robinson
	Anne	Todd
	Patricia	Turner
	Sally	Young
Mount Vernon Hospital	Mark	Harrison (PI)
	Farhan	Ahmed
	Nicola	Anyamene
	Nicky	Barnes
	Neel	Bhuva
	Sam	Bosompem
	Kari	Evans
	Shiv	Gayadeen
	Rob	Glynne-Jones
	Marcia	Hall
	Rakhi	Jain
	Colleen	Murray
	Julie	Russell
	Waqar	Saleem

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Anand	Sharma
	Margaret	Stone
	Harsha	Vara
Queen Elizabeth Hospital (Birmingham)	Gary	Middleton (PI)
	Sabia	Akhtar
	Amisha	Desai
	Colm	Forde
	Kam	Gareja
	Sharon	Hackett
	Sam	Hopkins (nee Poole)
	Mary	Kotadia
	Victoria	Kunene
	Catherine	Prest
	Helen	Preston
	Donna	Smith
	Phillipe	Taniere
Queen's Hospital Burton	Manjusha	Keni (PI)
	Ann	Adams
	Mosan	Ashraf
	Jo	Burns
	Helen	Cox
	Katy	English
	Annette	Fleet
	Sarah	Hathaway-Lees
	Elizabeth	Kemp
	Hayley	Lewis
	Clare	Mewies
	Jennifer	Moyes
	James	Price
	Scott	Sanders
	Adrian	Smith
	Alison	Tilley
Russells Hall Hospital	Ankit	Jain (PI)
	Simon	Grumett (PI)
	Joann	Atkinson
	Daniel	Bull
	Donna	Cleal
	Lesley	Edwards
	Kath	Harrow
	Stacey	Jennings

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Lucy	Kadiki
	Karen	Kanyi
	Sally	Keates-Porter
	Pek	Keng-Koh
	Margaret	Marriott
	Julie	Matthews
	Karen	McGarry
	Vanessa	Moore
	Andrew	Moores
	Manesh	Patel
	Veena	Shinde
	Lucie	Smith
	Lucy	Smith
	Angela	Watts
Singleton Hospital	Sarah	Gwynne (PI)
	Cristina	Lopez (PI)
	Alya	Al-Affan
	Philip	Bryant
	Karen	Chesters
	Sharon	Davies
	Jenna	Edwards
	Stuart	Evans
	Tracey	Ford
	Ricky	Frazer
	Judith	Gooding
	Olivia	Hatcher
	Gillian	Jones
	Lewis	Jones
	Maung	Moe
	Karen	Phillips
	Euan	Pratt
	Alex	Richards
	Louise	Thomas
	Julie	Turner
	Nia	Viney
	Dawn	Withers
University Hospital Coventry	Vanessa	Potter (PI)
	Jason	Allen
	Senthil Kumar	Athmanathan
	Rachel	Bazeley
	Susan	Bird

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Yasmin	Brough
	Maggie	Brown
	Dannielle	Burgess
	Luanne	Carey
	Philippa	Clark
	Peter	Correa
	Kishore	Gopalakrishnan
	Cheryl	Hunter
	Sian	Kempster
	Mohammed	Khan
	Fiona	McGurk
	Jade	McKelvie
	Lucy	Miller
	Sarah	O'Toole
	Karandeepu	Pachoo
	Noor	Shaw
	Laura	Stanley
	Charlie-marie	Suddens
	Rachel	Thompson
	Maria	Truslove
	Linda	Wimbush
	Jane	Wording
University Hospital of North Tees	Madhavi	Adusumalli (PI)
	David	Wilson (PI)
	Alison	Chilvers
	Helen	Dunn
	Sarah	Essex
	Mohammad	Hegab
	Hyder	Latif
	Moira	Percival
	Sarah	Pitcairn
	Lynda	Poole
	Pam	Race
	Andrew	Sigsworth
	Eleni Andriana	Trigka
	Helen	Wardle
	Bill	Wetherill
Whittington Hospital (London)	Pauline	Leonard (PI)
	Rashidat	Adeniba
	Dhili	Arul
	Jonathan	Flor

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Kavita	Kantilal
	Xiao Lou	Lu
	Mulyati	Mohamed
	Michelle	Saull
	Nuray	Temiz
	Azmina	Verjee
	Simon	Wan
Freeman Hospital, Newcastle	Ashraf	Azzabi (PI)
	Craig	Alderson
	Chris	Barron
	Michelle	Borthwick
	Julie	Burton
	Kay	Carson
	Fiona	Chapman
	Sarah	Cook
	Fareeda	Coxon
	Sue	Farrell
	Elaine	Greaves
	Ahmed	Hashmi
	Amanda	Henderson
	Kathryn	Hewitt
	Ben	Hood
	Thomas	Jarvis
	Irene	Jobson
	Najibah	Mahtab
	Lesley	Naik
	Stephanie	Needham
	Gemma	O'Neill
	Ian	Pedley
	Sindhu	Ramamurthy
	Zarine	Razvi
	Elizabeth	Reay
	Timothy	Simmons
	Carole	Stobbart
	Jonathan	Stoddart
	Nichola	Waugh
	Hesther	Wilson
Leighton Hospital	Michael	Braun (PI)
	Vanessa	Adamson
	Carole	Bennion
	Kim	Best

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Leanne	Everall
	Julia	Gemmell
	Laura	Hanton
	Christy	Henderson
	Adele	Hough
	Chris	Hough
	Cyndy	Jackson
	Taya	Jones
	Tracy	Larcombe
	Carolyn	Mansfield
	Emma	Margerum
	Julie	Meir
	Andrew	Ritchings
	Paul	Simcock
	Sarah	Tinsley
	Caroline	Walker
Ninewells Hospital, Dundee	Sharon	Armstrong (PI)
	Jennifer	Allison
	Rachael	Banks
	Anne	Black
	Louise	Brannan
	Frank	Carey
	Shona	Carson
	Helen	Cumming
	Debbie	Forbes
	Audrey	Lyall
	AJ	Munro
	Moira	Rogers
	Ian	Sanders
	Gail	Weir
Westmorland General Hospital	David	Eaton (PI)
	Rebecca	Anderson
	Syed	Asghar
	Manal	Atwan
	Claire	Bartlett
	Ashoke	Biswas
	Jennifer	Bowler
	Karen	Burns
	Rebecca	Calvert
	Amy	Ford
	Laura	Healey

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Nima	Herlekar
	Maria	Kassi
	Lauren	Kilifin
	Jo	Kilkenny
	Nicola	Mackenzie
	Aileen	Menzies
	Helen	Morris
	Debbie	Power
	Jane	Ritchie
	Mary	Robinson
	Vickie	Rose
	Rachel	Simmons
	Andrew	Taylor
	Hilary	Thatcher
	Gail	Wiley
Belfast City Hospital	Victoria	Coyle (PI)
	Conal	Askin
	Ellen	Brown
	Karen	Campfield
	Catherine	Davidson
	Michael	Hanna
	Diane	Law
	Alison	McKeever
	Aine	McKeown
	Damian	McManus
	Linda	McNeice
	Karen	Parsons
	Miranda	Reid
	Fiona	Tarpey
	Joanne	Todd
	Paul	Ward
	Richard	Wilson
Dorset County Hospital	Amelie	Harle (PI)
	Richard	Osborne (PI)
	Pauline	Ashcroft
	Corrado	d'Arrigo
	Maxine	Flubacher
	Jackie	Gibbins
	Karen	Hogben
	Arabis	Oglesby
	Andrew	Rees
	Simon	Wilsher

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
Great Western Hospital	Sarah	Lowndes (PI)
	Graham	Brown
	Christopher	Clarke
	Amanda	Colston
	Jan	Dodge
	Eva	Fraile
	Sarah	Grayland
	Lesley	Haxton
	Lawrence	John
	Jean	Kordula
	Lynsey	Kyeremeh
	Donna	Lake
	Catherine	Lewis Clarke
	Sarah	Long
	Dorota	Marciniak
	Laura	McCafferty
	Darren	McFadden
	Sue	Meakin
	Chanelle	Meyer
	Tim	Owen
	Cerila	Parajes
	Ronak	Patel
	Suzannah	Pegler
	Caroline	Pensotti
	Joseph	Stevens
Milton Keynes University Hospital	Wasiru	Saka (PI)
	Ann	Abraham
	Hannah	Ansell
	Sam	Bosompem
	Matthew	Burnett
	Chris	Ford
	Chloe	Green
	Sara	Greig
	Penni	Hawkins
	Chamene	Hicks
	Aarzoo	Ilyas
	Charity	Masvaure
	Louise	Moran
	Mala	Nathvani
	Cheryl	Padilla-Harris
	Vijay	Patel

(continued on following page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Shahriar Mohammed	Reza
	Syed Azhar Javed	Rizvi
	Abby	Skillington
	Jeannette	Smith
	Oliver	Spring
	Heather	Thomas
	Stephanie	Thorp
	Valerie	Webb
	Dona	Wingfield
	Christopher	Woodard
New Cross Hospital	Simon	Grumett (PI)
	Syed	Asghar
	Vanda	Carter
	Sandeep	Dhillon
	Anna	Grant
	Clare	Hammond
	Kelly	Kauldhar
	Margaret	King
	Christine	Kirk
	Claire	Lomas
	Manel	Mangalika
	Gurminder	Sahota
	Elaine	Wylde
Pilgrim Hospital	Zuzana	Stokes (PI)
	Antoinette	Adu
	Simon	Archer
	Gloria	Barone
	Jayne	Borley
	Wendy	Deamer
	Jo	Fletcher
	Matthew	Flook
	Amy	Kirkby
	Victoria	Knight
	Tara	Lawrence
	Beverley	Mashegede
	Helen	Palmer
	Kerry	Pettitt
	Gunjan	Phalod
	Manuel	Ruiz-Echarri
	Gemma	Sankey
	Thomas	Sheehan

(continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Rebecca	Spencer
	Kinga	Szymiczek
	Isobel	Thomas
Rotherham District General Hospital	Joanne	Hornbuckle (PI)
	Matthew	Barnes
	Sarah	Besley
	Meredyth	Harris
	Kath	Lowe
	Scott	Nicol
	Susan	Oakley
	Amy	Rees
	Charlotte	Widdop
Royal Bournemouth Hospital	Tamas	Hickish (PI)
	Jocelyn	Ablorde
	Omolade	Bakarey
	Rachel	Bower
	Zoe	Clark
	Nicole	Davies
	Alison	Hogan
	Stephanie	Jones
	Tiffany	Joyce
	Maria	Lane
	Sharon	Megson
	Sandy	Pressdee
	Linda	Purandare
	Taslima	Rabbi
	Emma	Sharland
	Esther	Una Cidon
	Luke	Vamplew
	Jasmin	Webb
Royal Marsden Hospital (London)	Ian	Chau (PI)
	Helen	Breeze
	Shirley	Clifton
	Saoirse	Dolly
	Sandra	Esteban Moreno
	Lucy	Featherstone
	Shelby	Hatt
	Blanka	Hezelova
	Alexander	Lee
	Hazel	Lote

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Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])
	Lizzie	Love
	Nnenna	Ngwu
	Isma	Rana
	Gihan	Ratnayake
	Penny	Rogers
	Clare	Saffery
	Anna	Scott
	Izelle	Ueckermann
	Chloe	Westrip
	Ian	Chau
	Sally	Abdelmalik
	Gayahri	Anandappa
	Joo Ern	Ang
	Thushasa	Ansari
	Sheila	Azaiji-Benjamin
	Annette	Bryant
	Shirley	Clifton
	Richard	Crux
	David	Cunningham
	Sara	Diffley
	Julie	Duncan
	Laurice	Edwards
	Sandra	Esteban Moreno
	Lucy	Featherstone
	Monika	Ferencova
	Angela	Gillbanks
	Sarnjeet	Kaur
	Naila	Kaudeer
	Shelize	Khakoo
	Shannon	Kidd
	Retchel	Lazaro Alcausi
	Hazel	Lote
	Jacqueline	Oates
	Bijal	Patel
	Minal	Patel
	Brenda	Pem
	Sijy	Pillai
	Clare	Saffery
	Francesco	Sclafani
	Gillian	Smith
	Eleanor	Temple
	Jan	Thomas
	Andrea	Turner
	Izelle	Ueckermann
	David	Watkins

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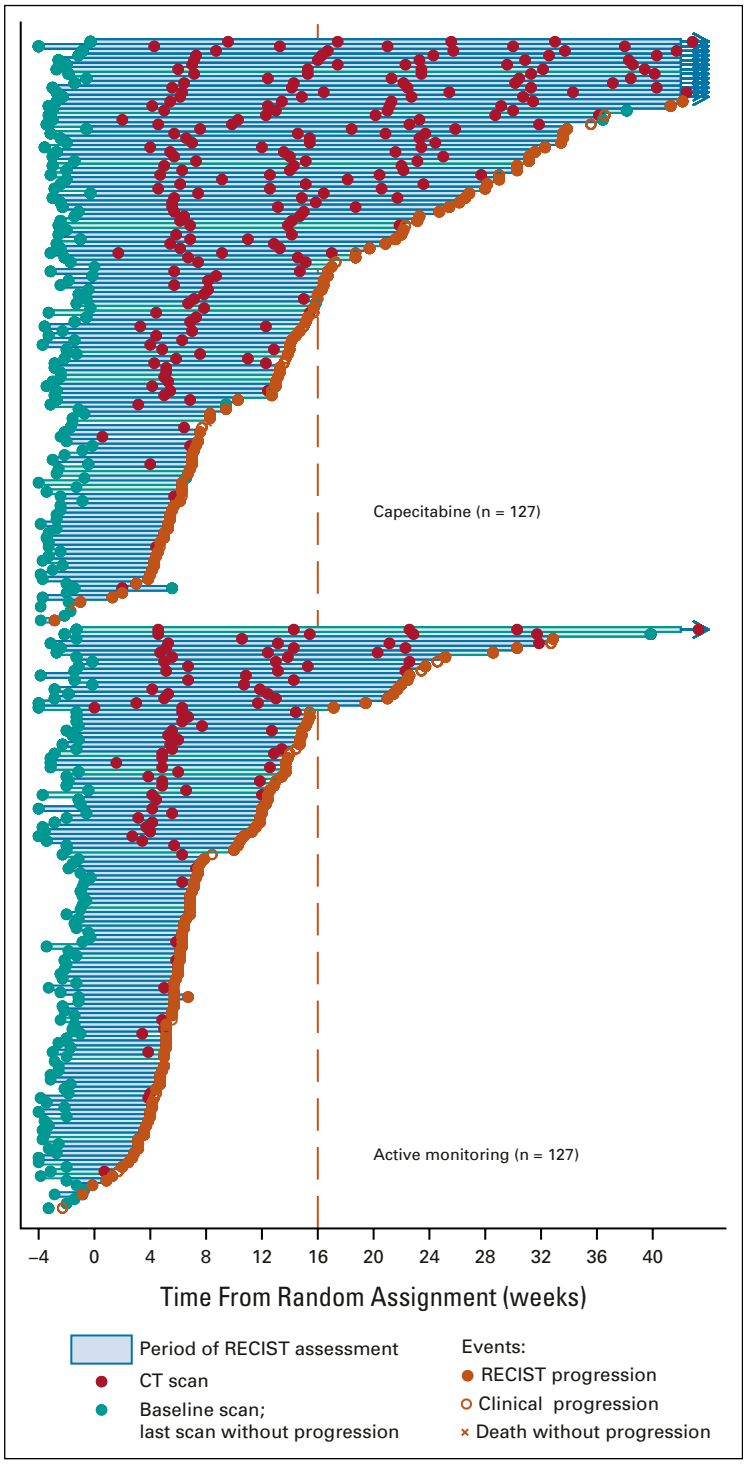

FIG A1. Swimmer plot for FOCUS4-N, by location of primary tumor. CT, computed tomography.

TABLE A1. Baseline Characteristics of Laboratory Tests by Treatment Allocation for FOCUS4-N

	Active Monitoring		Capecitabine	
		Mean (SD)		Mean (SD)
Characteristic	No.	Median (IQR)	No.	Median (IQR)
WBC, 10^9/L	127	6.3 (2.2)	127	6.6 (8.8)
		6.0 (4.6-7.4)		5.8 (4.9-7.6)
Neutrophils, 10^9/L	127	3.7 (1.8)	127	4.0 (3.4)
		3.4 (2.4-4.7)		3.5 (2.5-4.8)
Platelets, 10^9/L	127	244 (90)	127	249 (83)
		239 (190-284)		237 (184-294)
Serum bilirubin, mmol/L	127	8.7 (4.1)	127	8.3 (3.9)
		8.0 (6.0-11.0)		8.0 (5.0-10.0)
ALP, U/L	127	132 (79)	127	112 (60)
		110 (84-154)		98 (81-124)
AST/ALT, U/L	127	25.7 (14.5)	127	28.2 (17.5)
		22 (16-31)		24 (17-34)
Renal function, mL/min	126	90.5 (28.6)	127	90.5 (27.3)
		90 (69-100)		90 (71-101)
CEA, μg/L	122	96 (427)	125	83 (251)
		6 (3-28)		8 (3-22)
LDH, U/L	115	369 (149)	114	429 (489)
		353 (241-464)		376 (254-454)

Abbreviations: ALP, alkaline phosphatase; CEA, carcino embryonic antigen; IQR, interquartile range; LDH, lactate dehydrogenase; SD, standard deviation.

TABLE A2. Worst Toxicity Reported per Patient, by the Treatment Arm in FOCUS4-N

CTC Grade	Treatment Arm	
	Active Monitoring, No. (%) (n = 127)	Capecitabine, No. (%) (n = 127)
Nausea		
0	94 (74)	85 (67)
1	15 (12)	27 (21)
2	10 (8)	10 (8)
3	1 (1)	1 (1)
Missing	7 (6)	4 (3)
Vomiting		
0	106 (83)	108 (85)
1	7 (6)	9 (7)
2	6 (5)	5 (4)
3	1 (1)	1 (1)
Missing	7 (6)	4 (3)
Diarrhea		
0	92 (72)	58 (46)
1	19 (15)	40 (31)
2	6 (5)	19 (15)
3	3 (2)	6 (5)
Missing	7 (6)	4 (3)
Stomatitis		
0	114 (90)	98 (77)
1	5 (4)	21 (17)
2	1 (1)	4 (3)
Missing	7 (6)	4 (3)
Dry skin		
0	105 (83)	81 (64)
1	14 (11)	38 (30)
2	1 (1)	3 (2)
3	0 (0)	1 (1)
Missing	7 (6)	4 (3)
Skin rash		
0	111 (87)	104 (82)
1	9 (7)	14 (11)
2	0 (0)	3 (2)
3	0 (0)	2 (2)
Missing	7 (6)	4 (3)
Nail dystrophy		
0	110 (87)	105 (83)
1	9 (7)	16 (13)
2	1 (1)	2 (2)
Missing	7 (6)	4 (3)

(continued in next column)

TABLE A2. Worst Toxicity Reported per Patient, by the Treatment Arm in FOCUS4-N (continued)

CTC Grade	Treatment Arm	
	Active Monitoring, No. (%) (n = 127)	Capecitabine, No. (%) (n = 127)
PPE		
0	111 (87)	56 (44)
1	5 (4)	35 (28)
2	4 (3)	25 (20)
3	0 (0)	7 (6)
Missing	7 (6)	4 (3)
Anemia		
0	88 (69)	69 (54)
1	20 (16)	43 (34)
2	11 (9)	9 (7)
3	1 (1)	3 (2)
Missing	7 (6)	3 (2)
Neutropenia		
0	114 (90)	115 (91)
1	3 (2)	4 (3)
2	0 (0)	2 (2)
3	0 (0)	2 (2)
4	2 (2)	1 (1)
Missing	8 (6)	3 (2)
Total	127 (100)	127 (100)

Abbreviation: PPE, palmar-plantar erythema.