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Clinical Trial

A randomised, open-label phase II trial of afatinib versus cetuximab in patients with metastatic colorectal cancer

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Abstract ***Purpose:*** This randomised phase II trial aimed to compare efficacy of the irreversible ErbB family blocker, afatinib, with cetuximab in patients with KRAS wild-type metastatic colorectal adenocarcinoma (mCRC) with progression following oxaliplatin- and irinotecan-based regimens. Efficacy in patients with KRAS mutations was also evaluated.
Patients and methods: Patients with KRAS wild-type tumours were randomised 2:1 to afatinib (40 mg/day, increasing to 50 mg/day if minimal toxicity) or cetuximab weekly (400 mg/m^2 loading dose, then 250 mg/m^2/week) according to number of previous chemotherapy lines. All patients with KRAS-mutated tumours received afatinib. Primary end-points were

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objective response (OR) for the wild-type group and disease control for the KRAS-mutated group. Secondary end-points were progression-free survival (PFS) and overall survival (OS).
Results: Patients with KRAS wild-type tumours ($n = 50$) received afatinib ($n = 36$) or cetuximab ($n = 14$). Unconfirmed and confirmed ORs were 3% and 0% for afatinib versus 20% and 13% for cetuximab (odds ratio: 0.122 [$P = 0.0735$] and <0.001, respectively). Median PFS was 46.0 and 144.5 days for afatinib and cetuximab, respectively. Median OS was 355 days with afatinib but not reached for cetuximab. In the KRAS-mutated group ($n = 41$), five (12%) patients achieved confirmed disease control (stable disease; $P = 0.6394$ [comparison versus 10%]); no ORs were reported. Median PFS and OS were 41.0 and 173 days, respectively. Most frequent treatment-related adverse events were diarrhoea and rash across groups.
Conclusions: The efficacy of afatinib was inferior to cetuximab in patients with KRAS wild-type mCRC. In patients with KRAS-mutated tumours, disease control was modest with afatinib. Afatinib had a manageable safety profile.

1. Introduction

Signalling alterations mediated through the family of epidermal growth factor receptors (EGFR; ErbB) are implicated in the molecular pathogenesis of colorectal cancer (CRC), with overexpression linked to tumour progression and poor prognosis [1–3]. Moreover, EGFR, ErbB2 (human epidermal growth factor receptor 2 [HER2]) and ErbB4 have been shown to harbour somatic mutations associated with CRC development [4–7].

Several studies have shown that the effectiveness of anti-EGFR antibodies such as cetuximab and panitumumab was dependent on the Kirsten rat sarcoma viral oncogene homolog (KRAS) status of patients' tumour; patients treated with either of these agents and who had wild-type CRC had a better response and survival than those with KRAS-mutated tumours [8–12]. More recently, cetuximab plus chemotherapy improved outcomes in metastatic CRC (mCRC) patients expressing the specific KRAS G13D mutation, which has been shown to impact response to therapy [13].

The lack of benefit observed in patients with KRAS-mutated tumours treated with an EGFR inhibitor seems to be due to intrinsic resistance [8,14,15]. Even in patients with KRAS wild-type tumours, secondary (acquired) resistance to anti-EGFR therapy invariably develops [15,16]. Proposed mechanisms of acquired resistance to cetuximab involve increased EGFR activity (dysregulation of internalisation/degradation) and subsequent EGFR-dependent activation of HER2 and ErbB3 [17]. Also, ErbB3 activity, dependent on EGFR and HER2, represents a critical step for cells to escape cetuximab inhibition. Therefore, a high unmet medical need exists in mCRC.

Colorectal tumours generally lack 'addiction' to a single oncogenic signalling pathway for their survival and growth; therefore, sole inhibition of the EGFR pathway is unlikely to be as effective as blocking signalling mediated through the ErbB family. Afatinib is a highly selective, oral, irreversible ErbB family blocker, which blocks signalling from EGFR, HER2 and ErbB4 and transphosphorylation of ErbB3 [18,19].

Afatinib monotherapy has shown encouraging clinical efficacy in several cancers characterised by ErbB family overexpression including non-small cell lung cancer, squamous cell carcinoma of the head and neck and other cancers [20–26]. With potent activity against ErbB family members, afatinib may offer advantages over anti-EGFR monoclonal antibodies or EGFR tyrosine kinase inhibitors in CRC. Preclinical models indicate that afatinib inhibits growth of KRAS mutation-bearing CRC cell lines [27].

This phase II, multicentre, open-label study aimed to compare the efficacy of single-agent afatinib with cetuximab in patients with KRAS wild-type tumours who had failed both oxaliplatin- and irinotecan-based regimens, and to assess the efficacy of afatinib in patients with KRAS-mutated tumours.

2. Methods

2.1. Study design

There were three treatment arms in this study; patients with KRAS wild-type tumours were randomised in a 2:1 ratio to either afatinib (arm A) or cetuximab (arm B), with stratification according to previous lines of palliative chemotherapy received ($\leqslant 1$ or >1 line) and patients with KRAS-mutated tumours were all assigned to afatinib (arm C).

The study was conducted in the United Kingdom (UK) in accordance with the Declaration of Helsinki, local laws and the International Conference on Harmonisation Good Clinical Practice Guideline, and approved by relevant regulatory and independent ethics

committees or institutional review boards. All patients provided written informed consent.

2.2. Study population

Eligible patients were aged ⩾18 years with histologically or cytologically proven metastatic colorectal adenocarcinoma which was not amenable to potentially curative treatment, measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, Eastern Cooperative Oncology Group performance status of 0 or 1 and a life expectancy ⩾3 months. Patients must have failed both oxaliplatin- and irinotecan-based regimens, whether given in the adjuvant or palliative setting; patients with persistent peripheral neuropathy secondary to prior oxaliplatin who were deemed unsuitable for further oxaliplatin but whose disease had not progressed on the oxaliplatin-based regimen, were eligible. Patients were also required to have adequate baseline renal and hepatic functions and haematological values, a tumour sample available for KRAS-mutation testing and other biomarker analyses (re-testing of KRAS status was not required if this had been done by a certified laboratory and if the remaining sample was adequate for other biomarker analyses). Patients must have completely recovered from toxicities related to previous treatment (with the exception of peripheral neuropathy which must have improved to grade ⩽2), which must have been completed <12 weeks before study entry.

Exclusion criteria included: prior treatment with EGFR-targeting small molecules or antibodies; radiotherapy or surgery (other than biopsy) <4 weeks prior to study entry; untreated or symptomatic brain metastases or other current or history of malignancy (previous 5 years); known pre-existing interstitial lung disease; acute gastrointestinal disorders with diarrhoea as a major symptom; clinically relevant cardiovascular abnormalities, cardiac left ventricular ejection fraction <50%, or other concomitant serious illness or organ dysfunction that would in the investigator's opinion compromise study participation; contraindications to cetuximab; and biological therapy (including bevacizumab or any other anti-angiogenic agents) <4 weeks before study entry.

2.3. Treatment

Afatinib was started at 40 mg daily orally, and increased to 50 mg daily after 4 weeks if it was well tolerated, or reduced in steps of 10 mg in the event of any drug-related adverse events (AEs) to a minimum of 20 mg. Cetuximab treatment (given intravenously), including dose modifications, was consistent with the licensed indication; loading dose with 400 mg/m^2 on day 1, then 250 mg/m^2 once a week, weekly [28]. Treatment continued until disease progression, intolerability or study withdrawal for other reasons.

2.4. End-points

The primary end-point was objective response (OR; complete response [CR], partial response [PR]) in patients with KRAS wild-type tumours (arms A and B) and disease control (DC; CR, PR, stable disease [SD]) in arm C (patients with KRAS-mutated tumours). Response was evaluated every 6 weeks from treatment start regardless of delays or interruptions, according to RECIST 1.1 [29] and was investigator-assessed based on objective evidence only.

Secondary end-points included progression-free survival (PFS) and overall survival (OS). AEs were graded according to the Common Terminology Criteria for Adverse Events Version 4.0, and afatinib pharmacokinetics were determined. For afatinib-treated patients, limited blood sampling was performed to estimate trough plasma concentrations at steady state. Plasma concentrations were analysed by a validated high-performance liquid chromatography tandem mass spectrometry method at BI Pharma GmbH & Co. KG, Drug Metabolism and Pharmacokinetics Germany, Biberach, Germany. An explorative analysis of biomarkers was also undertaken.

2.5. Statistical methods

All analyses were descriptive and exploratory by nature. Simulated binomial distributions were used to calculate the sample population of patients with KRAS wild-type tumours to be randomised to afatinib ($n = 32$) and cetuximab ($n = 16$). For patients with KRAS mutations, it was calculated that a sample size of 40 would have 81.8% power to distinguish between DC rates of 10% (historical) and 25% (desirable).

To assess the likelihood of achieving OR for afatinib versus cetuximab, the primary analysis for the subgroup with KRAS wild-type tumours used logistic regression stratified by lines of palliative chemotherapy (⩽1 line or >1 line) to calculate the odds ratio and corresponding Wald 90% confidence interval (CI). For those with KRAS-mutated tumours, the Clopper-Pearson exact binomial 90% CI for the proportion of patients achieving DC was calculated and the exact binomial test applied to compare the proportion to the hypothesised value of 10%.

PFS and OS were summarised descriptively, and Kaplan–Meier plots produced.

3. Results

3.1. Patient characteristics

From July 2010 until March 2012, of 120 patients screened from 13 UK centres, 94 were entered. A total of 91 patients were treated as three were ineligible (Fig. 1). Of 51 patients with KRAS wild-type tumours,

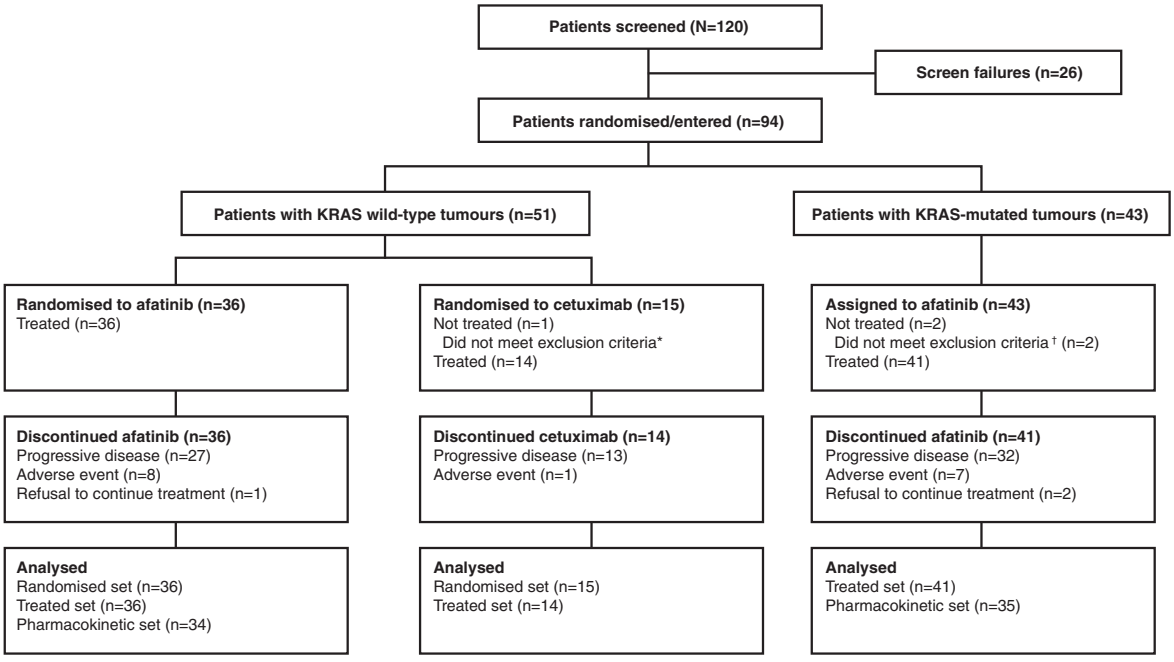

Fig. 1. Disposition of patients randomised to treatment. *Patient had an absolute neutrophil count <1500/mm^3 and was withdrawn prior to receiving study treatment. †Patient did not have a baseline Eastern Cooperative Oncology Group performance status of 0 or 1.

50 were randomised to receive either afatinib ($n = 36$) or cetuximab ($n = 14$), and 41 of 43 entered with KRAS-mutated tumours received afatinib (Fig. 1). All patients had received prior therapy, with the majority (81–88%) receiving >1 line of palliative chemotherapy (Table 1).

3.2. Treatment duration

In the KRAS wild-type group, patients received afatinib for a median of 48 days (range 2–182) and cetuximab for a median of 141 days (range 1–456). In the KRAS-mutated group, the median duration of afatinib treatment was 42 days (range 4–141).

3.3. Efficacy

3.3.1. KRAS wild-type tumours

There was no CR. One (3%) afatinib- and three (20%) cetuximab-treated patients had an unconfirmed PR (odds ratio: 0.122; $P = 0.0735$: 90% CI = 0.018–0.844) (Table 2). Confirmed OR were 0% with afatinib and 13% (two patients) with cetuximab (odds ratio = <0.001; P value and 95% CI were not estimable).

Median PFS was 46 days for afatinib- and 144.5 days for cetuximab-treated patients (Fig. 2). Median OS was 355 days among afatinib-treated patients and was not reached for cetuximab as patients were not followed up until time of death in this study (Fig. 2).

3.3.2. KRAS-mutated tumours

Five patients (12%) had a best response of SD ($P = 0.6394$; 90% CI = 4.9–23.9%; Table 2), congruent with the unconfirmed responses. Median PFS was 41 days and median OS was 173 days (Fig. 2).

3.4. Safety and tolerability

The safety profile was as expected for all treatment groups, with the majority of patients experiencing at least one treatment-related AE. In the KRAS wild-type group, 35 patients (97%) who received afatinib and all cetuximab-treated patients (100%) experienced treatment-related AEs; in the KRAS-mutated group, 39 patients (95%) experienced treatment-related AEs (Table 3). The most frequent treatment-related AEs (>15% of patients; Table 3) observed in patients who received afatinib were diarrhoea, rash, nausea, fatigue, vomiting and decreased appetite; whilst in cetuximab-treated patients, rash, diarrhoea, headache, nausea, decreased appetite, lethargy and hypomagnesaemia occurred.

In this study, the following AEs of special interest were evaluated as class effects of EGFR inhibitors: diarrhoea, rash and stomatitis. Treatment-related diarrhoea was more common in patients treated with afatinib (75% in Arm A, and 63% in Arm C) than in patients treated with cetuximab (29%; Table 3). However, rash was more common in the cetuximab arm (71%) than in either Arm A (56%) or Arm C (61%). Dermatitis acneiform as a separate AE to rash, and stomatitis, were observed in approximately similar proportions of patients in all three arms: 14% in arms A and B for both AEs and in arm C, 12% and 17% of patients experienced dermatitis acneiform and stomatitis, respectively (Table 3).

Table 1
Demographic and baseline characteristics of patients who were treated.

Characteristic	Patients with KRAS wild-type tumours		Patients with KRAS-mutated tumours
	Afatinib ($N = 36$)	Cetuximab ($N = 14$)	Afatinib ($N = 41$)
Gender, %			
Male	75	64	46
Female	25	36	54
Age, median years (range)	64.0 (39–81)	62.0 (46–73)	63.0 (32–78)
ECOG performance score, %			
0	53	36	41
1	47	64	59
Primary cancer site, %			
Caecum	11	7	10
Ascending colon	19	0	20
Transverse colon	6	21	7
Descending colon	3	0	2
Sigmoid colon	31	21	29
Rectum	31	50	32
Number of metastatic sites, mean (SD)	2.5 (1.0)	3.0 (1.1)	3.1 (2.6)
Previous treatment, %			
Surgery	81	86	68
Chemotherapy	100	100	100
Radiotherapy	28	43	37
Other	14	7	2
Previous lines of palliative chemotherapy, %			
$\leqslant$1 line	19	14	12
>1 line	81	86	88

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Overall, one afatinib-treated patient bearing a KRAS-mutated tumour experienced grade 4 dyspnoea and no grade 5 AEs occurred.

Most patients discontinued treatment owing to progressive disease, whilst AEs and refusal to continue treatment were minority reasons. In the KRAS wild-type group, six (17%) afatinib-treated patients discontinued owing to treatment-related diarrhoea ($n = 3$), vomiting ($n = 1$), lethargy ($n = 1$), decreased appetite, dehydration, lethargy, diarrhoea and nausea ($n = 1$). No patients discontinued cetuximab because of treatment-related AEs. In the KRAS-mutated group, there was a similar proportion of treatment-related discontinuations ($n = 8$; 20%): diarrhoea and/or nausea and vomiting ($n = 4$), decreased performance status, dyspnoea, proteinuria and lethargy with palmar-plantar erythrodysaesthesia syndrome (one patient each).

Overall, 18 patients experienced drug-related serious AEs: nine in the KRAS wild-type group (afatinib, $n = 8$ [22%]: vomiting [$n = 5$] and diarrhoea [$n = 4$]; cetuximab, $n = 1$ [7%]: fatigue), and 9 in the KRAS-mutated group (nausea and diarrhoea [3 patients each], and vomiting [$n = 2$]).

Thirteen patients died during the study: five with wild-type KRAS tumours (afatinib, $n = 3$; cetuximab, $n = 2$) and eight with KRAS-mutated tumours. None of the deaths were treatment-related and were mainly due to disease progression or disease-associated complications.

3.5. Afatinib pharmacokinetics

Pharmacokinetic data were insufficient to perform descriptive statistics other than for afatinib 40 mg. Steady-state afatinib 40 mg plasma concentrations achieved within 8 days remained stable over time. Individual and geometric mean plasma concentration–time profiles for afatinib 40 mg showed considerable variability in patients with KRAS wild-type ($n = 28$) and KRAS-mutated ($n = 24$) tumours, but no large differences were observed between the tumour types.

3.6. Biomarker analyses

In the subgroup of patients with KRAS-mutated tumours where a specific KRAS mutation was identified ($n = 32$), nine patients with KRAS G13D mutation (Gly13Asp) were included and received afatinib. Patients with tumours bearing a KRAS G13D mutation did not demonstrate a better best overall response or increased PFS versus those with a KRAS codon 12 mutation (data not shown).

Table 2
Best overall response, according to RECIST 1.1.

Best overall response (unconfirmed) *n*	Patients with KRAS wild-type tumours		Patients with KRAS-mutated tumours
	Afatinib ($N = 36$)	Cetuximab ($N = 15$)	Afatinib ($N = 41$)
Objective response	1	3	
Complete response	0	0	0
Partial response	1	3	0
	Odds ratio = 0.122; 90% CI = 0.018–0.844; $P = 0.0735$[a]		
Stable disease	10	7	5
Progressive disease	18	0	21
Not evaluable[b]	7	5	15
Disease control	–	–	5
			90% CI = 4.9–23.9; $P = 0.6394$[c]

CI, confidence interval; RECIST, Response Evaluation Criteria In Solid Tumours.
[a] Logistic regression stratified by the number of lines of palliative chemotherapy (⩽1 or >1 line); Wald Chi-square test and CI.
[b] RECIST tumour evaluation could not be performed. In the majority of these cases the patients progressed rapidly after randomisation and did not have a follow-up scan.
[c] Exact CI for rate and exact binomial test for comparison versus 10%.

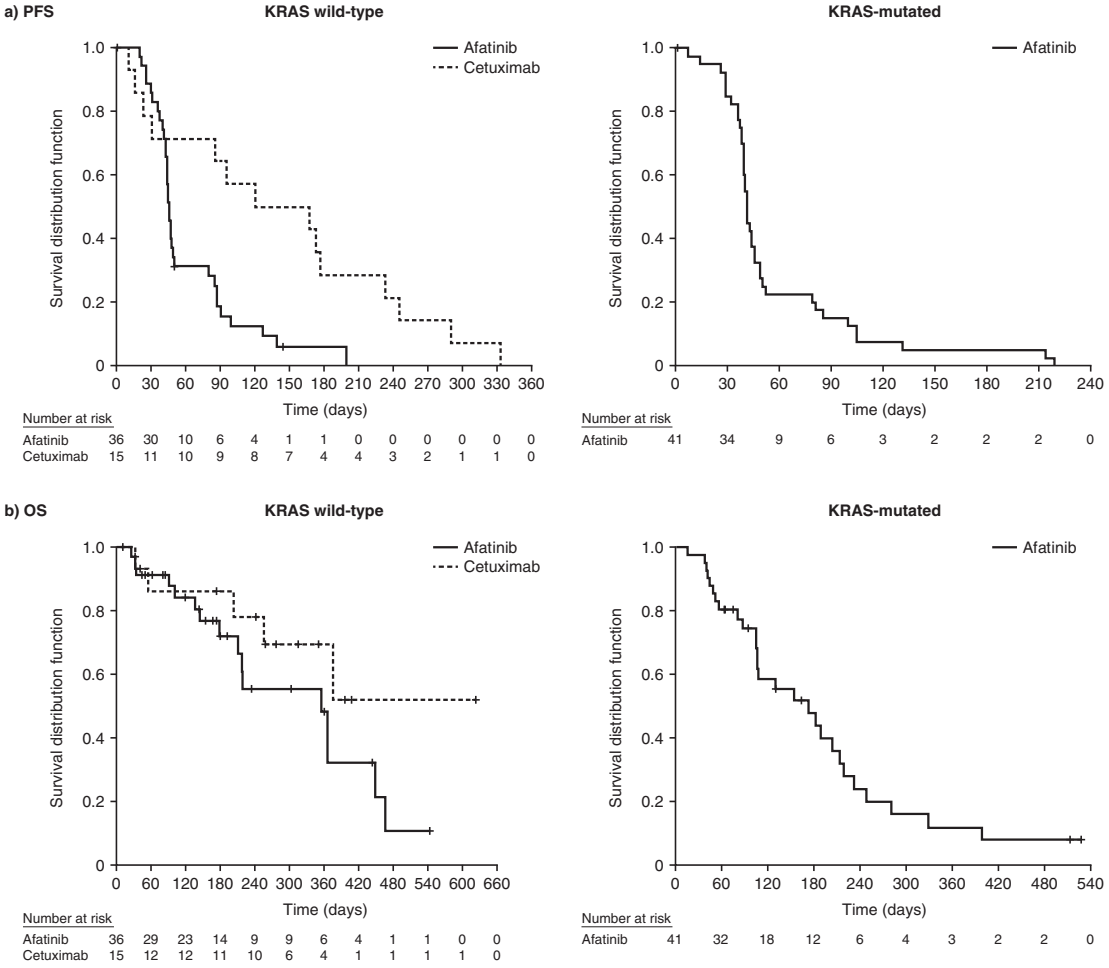

Fig. 2. Kaplan–Meier plot of (a) PFS and (b) OS in treated patients with KRAS and mutated tumours. Progression-free survival (PFS) was defined as the number of days from the randomisation date (group with KRAS wild-type tumours) or from the date of first afatinib dose (group with KRAS-mutated tumours) to the date of progression or death, whichever occurred first. Overall survival (OS) was defined as the number of days from the date of randomisation (group with KRAS wild-type tumours) or from the date of first afatinib dose (group with KRAS-mutated tumours) to the date of death.

Table 3
Treatment-related adverse events occurring in >10% of patients treated with afatinib.

	Patients with KRAS wild-type tumours				Patients with KRAS-mutated tumours	
	Afatinib ($N = 36$) %		Cetuximab ($N = 14$) %		Afatinib ($N = 41$) %	
	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3
Patients with any treatment-related adverse event	97	36	100	36	95	32
Adverse event						
Diarrhoea	75	8	29	0	63	12
Rash	56	6	71	29	61	0
Nausea	36	6	21	0	44	5
Fatigue	31	8	14	0	29	2
Vomiting	31	6	7	0	32	2
Decreased appetite	19	3	21	0	20	0
Oral pain	17	0	0	0	5	0
Epistaxis	14	0	0	0	7	0
Stomatitis	14	3	14	0	17	0
Dermatitis acneiform	14	0	14	0	12	0
Dysgeusia	11	0	0	0	10	0

4. Discussion

Development of innate or acquired resistance to anti-EGFR therapies prompts the continued search for alternative treatment strategies for patients with KRAS wild-type and -mutated mCRC. In this study, afatinib demonstrated inferior response and survival compared with cetuximab in patients with KRAS wild-type tumours. In patients with KRAS-mutated tumours there was no OR to afatinib, which is consistent with other studies of last-line treatment of KRAS-mutated colorectal patients with single-agent EGFR inhibitors [8,12]. The response rate to cetuximab observed here is similar to that reported in other patients with KRAS wild-type tumours, approximately 13–17% [8,12]. Patients were treated until disease progression or intolerable AEs and most commonly, patients discontinued owing to disease progression, which occurred to a similar extent across all study arms. The present results parallel the demonstrated lack of efficacy of single-agent EGFR tyrosine kinase inhibitors, gefitinib and erlotinib in this patient population [30,31]. This also highlights that resistance to EGFR inhibitors is not necessarily through other HER receptor-driven pathways; indeed, recent data suggested that amplification of the MET receptor conferred resistance to anti-EGFR therapies [32].

Preclinical evidence demonstrating the inhibitory effect of afatinib on growth of KRAS mutation-bearing CRC cell lines [27] was not translated to notable clinical benefit in the present study. There is a paucity of clinical evidence in the literature showing an effect of compounds on KRAS-mutated CRC, but a recent study showed that, in comparison with chemotherapy alone, cetuximab plus chemotherapy significantly improved PFS and tumour response, but not OS, in patients expressing G13D, but not other KRAS mutations [13]. In contrast with the results reported by Tejpar et al. [13], the present study did not demonstrate a differential response between patients with tumours bearing a KRAS G13D mutation and those with a KRAS codon 12 mutation. Whether or not the small subgroup population or the single-agent approach accounted for the contrasting results would need further investigation.

Mutations in genes other than KRAS have been reported to affect response to anti-EGFR therapy. For example, NRAS and BRAF mutations have been associated with reduced response to EGFR inhibitors [33–35]. Whilst further data are needed to confirm these associations, meta-analyses have shown poor prognosis in mCRC patients with BRAF mutations [36,37]. Against this background, it would be of interest to compare afatinib with cetuximab in patients with/without mutations in genes such as NRAS and BRAF.

There were differences in the safety profiles of afatinib and cetuximab, potentially reflecting their respective mechanisms of action. AEs associated with cetuximab were in line with previous data [38], but with fewer events recorded in the present study, which may be related to the population size. Overall, afatinib had a manageable safety profile in line with known treatment-related AEs [39,40]. The most frequent treatment-related AEs in afatinib-treated patients were diarrhoea, rash, nausea, fatigue, vomiting and decreased appetite. Using an aggressive dose interruption and dose reduction scheme for afatinib, these AEs were appropriately managed and despite the high incidence of certain AEs such as diarrhoea, rash, nausea/vomiting, most of these events were mild (grade 1 or 2), with high grade (grade 3 or 4) AEs occurring in less than 10–12% of patients. The safety profile of afatinib was found to be consistent regardless of KRAS tumour status, as was the measured plasma concentration of afatinib; present data confirm

previous findings of no significant difference between afatinib plasma concentrations according to KRAS mutation.

Strengths and limitations should be noted in the interpretation of the study findings. Whilst the small patient numbers may appear to be a limitation, this study was appropriately powered to detect benefit. A strength of this study was the screening of patients with KRAS mutations and thus potential responders to EGFR inhibition as this represents the population with a high unmet need [41].

A further limitation of the present study was not controlling for the impact that previous therapy may have had on the clinical benefit observed with afatinib. Data from another drug in this class have shown that prior-treated patients with CRC demonstrate little response to gefitinib plus chemotherapy [42,43]. Whilst the present study has demonstrated a lack of clinical benefit of afatinib monotherapy, future studies could investigate the effect of afatinib combination therapy for CRC, particularly combination with other EGFR monoclonal antibodies where the potential for a synergistic effect exists.

5. Conclusions

In this phase II study, the efficacy of afatinib was inferior to cetuximab in patients with KRAS wild-type tumours. A modest effect of afatinib was seen in patients with KRAS-mutated tumours. Afatinib had a manageable safety profile, which was unaffected by KRAS mutation status.

Conflict of interest statement

I. Chau has received consultancy payments from Sanofi, Roche, Merck-Serono, Bristol-Myers Squibb and Eli Lilly, honoraria payments from Sanofi, Roche and Taiho, and grants from Sanofi, Roche and Merck-Serono. V. Potter has received funding from Boehringer Ingelheim to attend the British Thoracic Oncology Group Annual Conference. I. R. Macpherson has received honoraria and consultancy payments from Roche. H. Finnigan, C. Lee and H. Jones are employees of Boehringer Ingelheim. All remaining authors have declared no conflict of interest.

Role of funding source

Boehringer Ingelheim sponsored this trial and provided financial support for editorial assistance from Ogilvy Healthworld and GeoMed, part of KnowledgePoint360, an Ashfield Company. Of the Boehringer Ingelheim authors, C.L. and H.J. contributed to the study design. All authors contributed to data analysis/interpretation and the drafting, editing and finalisation of the manuscript.

Authors' contributions

T.H. was the Principal Investigator of the trial. T.H., C.L., J.C. and H.J. contributed to study design. T.H., J.C., D.P., I.C., S.F., H.Fo., T.I., M.B., V.P., I.M. and M.H. were responsible for data acquisition. T.H., J.C., D.P., I.C., S.F., I.M., H.Fi., C.L. and H.J. were responsible for data analysis and interpretation. H.Fi. was responsible for statistical analysis. T.H., H.Fi., C.L. J.C. and H.J. were responsible for manuscript preparation. All authors were responsible for editing, reviewing and finalising the manuscript, and approved the submitted version.

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