Investigating the poor outcomes of *BRAF*-mutant advanced colorectal cancer to develop practical treatment strategies

Jenny F. Seligmann[1], David Fisher[2], Christopher G. Smith[3], Susan D. Richman[1], Faye Elliott,[1] Sarah Brown[4], Richard Adams[3], Tim Maughan[5], Philip Quirke[1],Jeremy Cheadle[3], Matthew Seymour[1*] and Gary Middleton[6*].

Corresponding Author

Professor Gary Middleton
Institute of Immunology and Immunotherapy, University of Birmingham and University Hospital Birmingham, UK
Tel: 44 7789502237
Email: G.Middleton@bham.ac.uk

Affiliations

1. Leeds Institute of Cancer and Pathology, University of Leeds, St. James's University Hospital, Beckett St., Leeds, United Kingdom, LS9 7TF.

2. Medical Research Council Clinical Trials Unit, University College London, London, London

3. Institute of Medical Genetics, Institute of Cancer and Genetics, Cardiff University, Cardiff, United Kingdom

4. Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK

5. CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Oxford

6. Institute of Immunology and Immunotherapy, University of Birmingham and University Hospital Birmingham, UK

* MTS and GM are joint senior authors

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Abstract

Background:

To improve strategies for the treatment of *BRAF*-mutant advanced colorectal cancer (aCRC) patients we examined individual data from patients treated with chemotherapy alone in three randomised trials to identify points on the treatment pathway where outcomes differ from *BRAF* wild-types.

Patients and Methods:

2530 aCRC patients were assessed from three randomised trials. End-points were progression free survival (PFS), response rate (RR), disease control rate (DCR), post-progression survival (P-PS) and overall survival (OS). Treatments included first-line oxaliplatin/fluorouracil (OxFU), and second-line irinotecan. Clinicians were unaware of *BRAF*-status

Results

231 patients (9.1%) had *BRAF*-mutant tumours. *BRAF*-mutation conferred significantly worse survival independent of associated clinicopathological factors known to be prognostic. Compared with wild-type, *BRAF*-mutant patients in COIN treated with first-line OxFU had similar DCR (59.2% vs 72%; adjusted OR=0.76,p=0.24) and PFS (5.7 vs 6.3 months; adjusted HR=1.14, p=0.26). Following progression on first-line chemotherapy, *BRAF*-mutant patients had a markedly shorter P-PS (4.2 vs 9.2 months, adjusted HR=1.69,p<0.001). *BRAF*-mutant status did not confer a disadvantage for patients without progression having planned chemotherapy-free intervals (OS adjusted HR=0.97, p=0.75).

Fewer *BRAF*-mutant patients received second-line treatment (33% *vs* 51%, p<0.001), but *BRAF*-mutation was not associated with inferior second-line outcomes (RR adjusted OR=0.56, p=0.45; PFS adjusted HR=1.01, p=0.93).

Conclusions

BRAF-mutant aCRC confers a markedly worse prognosis independent of associated clinicopathological features. Chemotherapy provides meaningful improvements in outcome throughout treatment lines. Post-progression survival is markedly worse and vigilance is required to ensure appropriate delivery of treatment after first-line progression. However, *BRAF*-mutant patients may still enjoy treatment breaks when not progressing.

Key messages

- This is the largest study of *BRAF*-mutant aCRC*. BRAF*-mutant aCRC patients derive similar relative benefit from chemotherapy as wild-types; poor prognosis is not primarily due to chemoresistance. Instead, the point at which outcomes differ is following progression on first-line chemotherapy. *BRAF*-mutant aCRC patients can benefit from treatment breaks when stable, and from second-line chemotherapy.

INTRODUCTION

The V600E activating mutation in *BRAF* (*BRAF*-mutant) is found in the tumours of 8-12% patients with advanced colorectal cancer (aCRC). *BRAF*-mutant aCRC is consistently associated with poor overall survival (OS) and progression free survival (PFS) in case series[1,2,3] and randomised controlled trials (RCTs).[4,5] In a recent RCT of previously untreated aCRC, median OS was 13.4 months in *BRAF*-mutant patients compared with 37.1 months in *RAS* and *BRAF* wild-types.[6] There is urgent need to optimise treatment strategies to improve outcomes in this population.

BRAF-mutant aCRC is well studied: most previous work has described poor prognosis, clinical characterisation, or assessment of sub-group outcomes in RCTs with chemotherapy combined with anti-EGFR agents or bevacizumab. However many important clinical and biological questions remain. Firstly the mechanism for the poor prognosis is poorly understood, and it is unclear at what point in the aCRC treatment pathway that *BRAF*-mutant outcomes diverge from wild-types; whilst OS is uniformly poor, less impact is seen with PFS compared with wild-types.[7,8,] It has been hypothesised that poor outcomes are secondary to intrinisc chemoresistance but there is a paucity of data describing the outcomes of *BRAF*-mutant aCRC with chemotherapy alone, particularly beyond the first-line.

Importantly previous publications have not performed careful multivariate analysis. This is critical as *BRAF*-mutant aCRC is associated with

clinicopathological features which are themselves negative prognostic factors,[9] including defective mismatch repair (dMMR) status[7,10], right sided primary tumour location (PTL)[11] and a high incidence of peritoneal metastases.[12] The observed poor outcomes may instead be driven by such factors so it is essential to prospectively factor this into analyses of outcomes. Only one study has adjusted *BRAF* outcomes by one of these factors, dMMR, and found poor outcomes to be independent of this.[7]

Detailed analysis of the natural history of *BRAF*-mutant aCRC will provide more clarity to patients and their physicians about prognosis and an evidence base to quantitate the benefits of different chemotherapy strategies throughout the treatment pathway. Ultimately this will help in devising strategies to maximise their outcomes.

Maximising outcomes with chemotherapy are particularly important in this aCRC sub-group, as the addition of other agents used in aCRC and trials of novel agents have been disappointing. *BRAF*-mutant status as a negative predictive marker for anti-EGFR agents has been controversial.[5,12] However, a recent meta-analysis comparing outcomes of *BRAF*-mutant patients in RCTs treated with anti-EGFR agents plus chemotherapy or chemotherapy alone reported an OS hazard ratio of 0.97, making it difficult to justify the added toxicity and cost.[14] Additionally the use of targeted agents to improve outcomes in *BRAF*-mutant aCRC have been disappointing, in contrast to succeses in melanoma.[15] Combined *BRAF* and MEK inhibition in a heavily pretreated *BRAF*-mut aCRC population, produced a median PFS was 3.5 months,[16]

contrasting with 9.4 months with the same combination in *BRAF*-mutant melanoma.[15] One promising strategy for this patient group is triplet chemotherapy plus bevacizumab,[6] but many patients will not be fit enough for this regimen. Thus, analysis of outcomes on doublet and singlet chemotherapy remains highly relevant.

We have examined individual patient data from three RCTs to identify points on the treatment pathway at which *BRAF*-mutant outcomes differ from *BRAF* wild-type patients treated with cytotoxic chemotherapy, to assess the impact of potential confounders and to provide clinicians with detailed information of outcomes with various chemotherapy strategies. We analysed treatment outcomes in two first-line RCTs with oxaliplatin/fluorouracil (OxFU), behaviour during chemotherapy-free intervals and following disease progression. We then report patterns of, and outcomes with second-line therapy. In order to avoid potential interactions of *BRAF* status with anti-EGFR drugs we focus on patients treated in arms that did not include targeted therapies. Potential confounding factors were prospectively identified, and analyses adjusted accordingly. *BRAF*-status was unknown to clinicians treating patients in each trial, eliminating potential bias.

PATIENTS AND METHODS:

Patient population and treatment:

Individual patient data were obtained from selected arms of three large randomised trials, to reflect different clinical uses of standard cytotoxic chemotherapy (without targeted therapy) in aCRC (Figure 1).

- FOCUS (ISRCTN 79877428) was a sequencing trial of first-line and planned second-line therapy, and provided a cohort of 430 patients receiving single-agent 5FU ahead of planned second-line irinotecan or oxaliplatin-based therapy, plus a cohort of 357 randomised to first-line doublet (IrFU or OxFU).[17]
- COIN (ISRCTN 27286448) provided a cohort of 1284 patients randomised to first-line oxaliplatin/fluoropyrimidine (OxFp) doublet either continuously (Arm A) or with planned chemotherapy-free intervals (Arm C).[18,19]
- PICCOLO (ISRCTN 93248876) provided a cohort of 511 OxFp-resistant patients treated with second-line irinotecan.[12,20]

Inclusion criteria for FOCUS and COIN were consistent and both patient groups were treated in centres in the UK. Full reports of these studies have been published.[12,17-20] National ethical approval and patient consent was obtained for all aspects of the clinical and translational research. DNA extraction and genotyping for mutations including *BRAF*$_{V600E}$ was performed retrospectively as previously reported.[12,21,22]

Statistical analysis

Stata was used (*Release 12 (2011)*, StataCorp. College Station, Texas). Baseline patient characteristics were compared between *BRAF*-mutant patients (with or without other MEK/AKT pathway mutations) and *BRAF* wild-type patients using two-tailed T-tests, Wilcoxon rank sum tests (for variables with non-normally distributed frequency distributions) and Pearson Chi-squared tests (for categorical variables).

In addition to OS (time from randomisation to death from any cause), three treatment-related clinical endpoints were used: PFS (time from randomisation to first evidence of progression or death); 12-week RECIST response rate (RR), and disease control rate (DCR).[23] Finally, we compared post-progression survival time (P-PS), defined as time from progression to death in those with a progression event, however when date of progression data was unavailable date of last chemotherapy cycle was used instead.

The prognostic influence of *BRAF*-mutant status on survival outcomes (PFS, P-PS and OS) for first-line trials (FOCUS and COIN), then the second-line trial (PICCOLO) were analysed using Cox proportional hazards modelling and described using hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for factors known to be prognostic or likely to interact with *BRAF*-status. In COIN and FOCUS these were: WHO performance status (2 vs 0/1); primary tumour resected (yes vs no); PTL (right colon vs other); platelet count (< vs ≥ 400,000/μl); peritoneal metastases (present vs absent) and mismatch

repair (MMR) status. In PICCOLO, adjustment was made for: response to previous therapy; performance status; peritoneal metastases; primary tumour resected and PTL. As these factors individually interact with prognosis, adjusted values are reported primarily but unadjusted values are provided.

Kaplan-Meier (KM) curves were plotted. For response endpoints, odds ratios (ORs) and 95% CIs were estimated from logistic regression models for the effect of *BRAF*-mutant status, adjusted for the markers previously described.

RESULTS

Clinicopathological variables associated with *BRAF*-mutant aCRC

BRAF status was available for 787/2135 (36.9%) patients in FOCUS, 1284/1630 (78.8%) in COIN and 459/511 (89.8%) in PICCOLO (Figure 1). The *BRAF*-mutant prevalence was consistent with published values (FOCUS 61/787 [7.8%], COIN 130/1284 [10.1%], PICCOLO 40/459 [8.7%]). *BRAF*-mutant patients were more likely than *BRAF* wild-type to be female, have right-sided PTL, have peritoneal metastases and nodal metastases, but less likely to have lung metastases. *BRAF*-mutant tumours were more likely to have dMMR than *BRAF* wild-type tumours (12.6% vs 3.0%, p<0.001). 8/2530 (0.3%) patients' tumours had dual mutations in both *BRAF* and *KRAS* (Table 1)

BRAF-status as a prognostic marker for overall survival

BRAF-mutant status was a significant prognostic marker for OS in both first-line studies (COIN 9.8 vs 16.6 months, unadjusted HR =1.78 [1.46-2.17], p<0.001; FOCUS 10.9 vs 16.2 months, unadjusted HR=1.55 [1.18-2.04], p=0.030)(Table 2). Combining these data [n=2071] gave a median OS of 10.8 vs 16.4 months (HR=1.49 [1.23-1.80] p<0.001)(Figure 2).

As *BRAF*-mutant status was associated with clinicopathological characteristics that may interact with survival (Table 1), their prognostic impact was explored in a univariate, then multivariate analysis in data pooled

from the first-line trials. Significant factors predicting poor OS on univariate testing were *BRAF*-mutant status, poor performance status, high platelet count, right PTL, peritoneal metastases, primary tumour *in-situ* and dMMR status; in multivariate testing, all factors remained significant other than dMMR status (Supplementary Table 1).

Following adjustment, *BRAF*-mutant status remained a significant prognostic marker in both trials (COIN adjusted HR =1.51 [1.19-1.91], p<0.001; FOCUS adjusted HR=1.44 [1.04-2.00], p=0.030)(Table 2). Given the demonstrated prognostic effect of clinicopathological factors associated with *BRAF*-mutant status all subsequent analyses are adjusted.

Impact of *BRAF*-status on treatment-related endpoints on first-line combination chemotherapy

In contrast to its marked effect on OS, *BRAF*-mutant status had modest or insignificant impact on the first-line PFS and response endpoints. Although, patients treated with first-line OxFP in COIN, *BRAF*-mutant patients had an inferior 12-week RR (34.3% vs 47.5%, adjusted OR=0.58 [0.37-0.92], p=0.020), the differences in DCR and PFS were not significant (DCR 59.2% vs 72.0%, adjusted OR=0.76 [0.49-1.20], p=0.24; PFS 5.7 vs. 6.3 months, adjusted HR=1.14 [0.91-1.42], p=0.26)(Table 2). There was no evidence of a differential effect of *BRAF* status according to the doublet used (OxFU or OxCap)(data not shown).

Similarly for patients treated with first-line combination chemotherapy in FOCUS, there were no differences in efficacy endpoints in *BRAF*-mutant compared with *BRAF* wild-type patients: PFS was 8.2 vs 8.8 months (adjusted HR=1.07 [0.69-1.67], p=0.75); RR was 43.7% vs 43.1% (adjusted OR=1.09 [0.45-2.65], p=0.85); DCR was 68.9% vs 69.9% (adjusted OR=1.01 [0.36-2.84], p=0.97)(Table 2). There was no evidence of a differential effect of *BRAF*-status according to regimen used (OxFU or IrFU, p=0.26).

Impact of *BRAF*-status on post-progression survival

Following progression on first-line combination chemotherapy, *BRAF*-mutant patients had markedly reduced P-PS compared with *BRAF*-wt in both first-line trials. In COIN PPS was 3.2 months in *BRAF*-mutant compared with 8.6 months in *BRAF*-wt patients (adjusted HR=1.72 [1.35-2.19], p<0.001). Similarly in FOCUS inferior P-PS was observed between *BRAF*-mutant and wild-types (3.2 vs 8.1 months; adjusted HR=1.65 [1.03-2.67], p=0.038)(Table 2). Combining this data P-PS was inferior in the *BRAF*-mutant compared with the *BRAF*-wt group (3.2 vs 8.6 months, HR=1.72 [1.35-2.19], p<0.001)(Figure 3). These marked differences were independent of first-line treatment received (in COIN, OxFU vs OxCap p=0.53, in FOCUS OxFU vs IrFU p=0.91)(data not shown).

When other prognostic factors were tested in a combined multivariate model, a significant negative effect on P-PS was seen after first-line chemotherapy for peritoneal metastases and dMMR status (peritoneal metastases HR=1.39,

p<0.0001; dMMR HR=1.38, p=0.025). However the negative prognostic impact of peritoneal metastases and dMMR appears limited to the *BRAF* wild-type population, and neither factor impacted further on the poor P-PS seen in *BRAF*-mutant patients (interaction p= 0.005 and p=0.05 respectively), showing that it is the *BRAF*-mutation driving the observed poor outcomes (Supplementary Table 2).

Impact of *BRAF* status on salvage therapy

To explore the mechanism for inferior first-line P-PS in *BRAF*-mutant patients, we studied uptake of post-progression therapies and survival outcomes of those who received second-line treatment, compared to those who did not.

In COIN, *BRAF*-mutant patients were less likely to receive second-line therapy after first-line progression (33% vs. 51%, p=0.0002). Similarly, after completion of the FOCUS plan, which for all patients included two drugs (FU and either oxaliplatin or irinotecan, given over 1 or 2 lines), 123/401 (30.7%) *BRAF* wild-type and 3/29 (10.3%) *BRAF*-mutant patients received subsequent salvage therapy (p=0.020)(data not shown).

The duration of second-line therapy (regimens including FU-based, Ir-based, oxaliplatin-based, cetuximab and bevacizumab) for those who received it, was unaffected by *BRAF*-mutant status (COIN p=0.55, FOCUS p=0.18). The only exception was the subgroup of FOCUS patients randomised to receive IrFU

after progression on FU alone, where *BRAF*-mutant status was associated with shorter treatment duration (p=0.019)(data not shown).

OS was improved in COIN for those who received subsequent second-line chemotherapy compared with those without, regardless of *BRAF*-status (*BRAF*-mut 16.1 vs 7.8 months [HR=0.56, p=0.005]; *BRAF* wild-type 21.1 vs 11.6 months [HR=0.48, p<0.001]; interaction p=0.66)(Figure 4). However *BRAF*-mutant patients had worse OS whether treated with second-line chemotherapy, (HR=1.91[1.36-2.69], p<0.001), or not (HR=1.44 [1.12-1.84], p=0.004), compared with wild-types.

Impact of chemotherapy-free intervals in *BRAF*-mutant patients

In contrast to the worse outcome after failure of first-line chemotherapy, there was no evidence that *BRAF*-mutant patients fare less well with a planned treatment break when first-line treatment has not yet failed. COIN, which compared continuous or intermittent chemotherapy strategies, found that intermittent chemotherapy in the entire population was non-inferior for OS (adjusted HR=1.04 [0.98–1.10], p=0.16).[19] In *BRAF*-mutant patients this was also the case (adjusted HR=0.97 [0.80–1.17], p=0.75) (Figure 4).

In all patients progression events in patients during chemotherapy breaks led to shorter PFS (adjusted HR=1.27 [1.21–1.33], p<0.001).[19] Interestingly, however, *BRAF*-mutant patients were the only molecular sub-group not to have a PFS disadvantage with intermittent chemotherapy (*BRAF*-mutant PFS

adjusted HR=1.09 [0.91–1.31], p=0.33; *BRAF*-wt PFS adjusted HR=1.29 [1.21–1.37], p<0.001; interaction p=0.14)(Figure 4).

Outcomes with single agent chemotherapy

We also examined the impact of *BRAF*-status on outcomes with single agent chemotherapy. With first-line single agent 5FU (n=430), PFS was similar in *BRAF*-mutant and *BRAF*-wt patients (6.5 vs 6.7 months; adjusted HR=0.96 [0.60-1.52], p=0.30); RR was 17.2% vs 21.7% (adjusted OR=0.54 [0.17,1.72], p=0.30); DCR 48.3% vs 60.6% (adjusted OR=0.72 [0.27-1.94], p=0.52)(Supplementary Table 3). Following progression on single agent 5FU, PPS was reduced in the *BRAF*-mutant group (3.5 vs 9.3 months; adjusted HR = 2.19[1.30-3.69],p=0.003)(Supplementary Table 3), again with a lower uptake of second-line therapies (39.3% vs 58.4%, p=0.048).

The impact of *BRAF*-status on outcomes for the 459 patients treated with second-line irinotecan was examined in the PICCOLO trial. Whilst OS was shorter for *BRAF*-mutant patients compared with *BRAF* wild-type, the difference did not reach statistical significance: 6.7 vs 10.2 months (adjusted HR=1.21 [0.84-1.76], p=0.31)(Supplementary Table 3 and Supplementary Figure 1). Similar to first-line data efficacy data and subsequent outcomes with salvage therapy, there were no significant differences between *BRAF*-mutant to *BRAF* wild-type patients in PFS (3.5 vs 4.0 months, adjusted HR=1.01 [0.69-1.49], p=0.93), RR (5.0% vs. 8.1%, adjusted OR=0.56 [0.13-

2.49], p=0.45)) and DCR (42.5% vs. 47.7% (adjusted OR=0.82[0.41-1.62], p=0.57)(Supplementary Table 3).

BRAF-mutant patients treated with anti-EGFR agents

The benefit of the addition of anti-EGFR agents to chemotherapy in COIN and PICCOLO has been previously reported. In COIN, whilst in PICCOLO BRAF-mut patients treated with IrPan had significantly shorter OS than those treated with Ir alone (interaction p=0.029). Whilst a less clear relationship was seen for PFS (IrPan vs Ir HR = 1.40, 0.82-2.39), but with negative interaction test there was a significant worsening of P-PS for patients treated with panitumumab who had mutation, compared with Ir alone. For these reasons we did not include this population in the primary analysis.

BRAF-mut treated with anti-EGFR agents had consistently inferior outcomes than *RAS*-wt patients in both trials. Within COIN *BRAF*-mut had inferior OS (7.2 vs 19.9 mths, HR=2.96[1.93-4.53], p<0.001), PFS (4.8 vs 9.3mths, HR=1.84[1.23-2.75], p=0.003), and markedly worse P-PS (1.9 vs 9.7 mths, HR=3.12 [2.14-4.54]). Similarly in PICCOLO (n=321) *BRAF*-mut patients had inferior OS (4.4 vs 11.1mths, HR=2.31[1.61-3.33],p<0.001), PFS (2.7 vs 5.5 mths, HR=1.70[1.24-2.61], p=0.002) and P-PS (3.2 vs 6.0 mths, HR=1.83[1.24-2.61], p=0.002).

DISCUSSION

This is the largest and most comprehensive clinical series assessing the outcomes of *BRAF*-mutant patients treated with chemotherapy at different points of the aCRC pathway. The poor outcomes of advanced *BRAF*-mutant aCRC are well described, but these cancers are associated with specific clinicopathological features: older age, right-sided primary tumour, high grade, deficient MMR, mucinous histology and peritoneal and lymph node metastases,[7,9-12] most of which interact with prognosis. In a careful multivariate analysis in a large, prospectively gathered cohort, *BRAF*-mutation still conferred a worse prognosis and is not simply attributable to associated clinic-pathological features.

A novel and striking finding is that this poor outlook is not driven by primary chemo-resistance, and that the point at which outcomes markedly diverge from wild-types is following progression on first-line chemotherapy. We observed no difference in the adjusted PFS between *BRAF*-mutant and wild-type patients receiving first-line chemotherapy or with second-line irinotecan monotherapy in our second-line trial. Similarly, we found no difference in the relative benefit of second-line therapy after failure of first-line chemotherapy. Results were consistent between both first-line trials, independent of chemotherapy strategy and other standard prognostic factors.

The combination of oxaliplatin and a fluoropyrimidine is a commonly used first-line therapy in aCRC. Other groups have shown that PFS on first-line

fluoropyrimidine is equivalent in *BRAF*-mutant and wild-type patients.[9] Furthermore, oxaliplatin may be particularly important in *BRAF*-mutant patients. Biomarker analysis from MOSAIC (testing the addition of oxaliplatin to FP in adjuvant treatment of early CRC) reported that the OS HR for OxFP vs FP alone was 0.55 in the *BRAF*-mutants, and 0.93 in wild-types.[24] The 3 year disease-free survival, 5 year OS and 10 year OS absolute differences for the addition of oxaliplatin were 16.4%, 9.5% and 10.1% respectively in *BRAF*-mut patients, compared with only 2.4%, 1% and 1.9% in wild-types.[24] In the TRIBE study (FOLFOXIRI plus bevacizumab vs FOLFIRI plus bevacizumab in the first-line treatment of aCRC), PFS HR for the addition of oxaliplatin to FOLFIRI/Bevacizumab in *BRAF*-mutant patients was 0.54, compared with 0.85 in *RAS/RAF* wild-types; the ORs for response was 1.82 and 1.17 respectively.[6] Biomarker analysis from the FOCUS trial, comparing first-line OxFU with FU alone produced HRs of 0.43 for PFS and 0.54 for OS in *BRAF*-mutant patients, compared with 0.68 and 0.86 respectively in *BRAF* wild-types.[21]

BRAF-mutant patients have markedly worse survival after progression on first-line treatment, with important implications for patient management. Second-line therapy provides equivalent relative benefits to wild-type patients and fewer *BRAF*-mutant patients receive second line therapy. It is important to emphasise that treating physicians were unaware of *BRAF*-status, so this finding is not due to selection bias. We therefore advocate extra vigilance when treating *BRAF*-mutant patients, to detect progression and rapidly institute second-line therapy, in the knowledge that this has the capacity to

significantly improve survival. One potential response to the observed rapid decline after first-line progression in *BRAF*-mutant patients would be to upgrade first-line therapy to a FOLFOXIRI-based regimen. However, only a subset of patients is fit enough to receive these more intensive treatments, instead many patients are routinely treated with doublets.

Equally importantly for routine practice, we found that whilst *BRAF*-mutant patients are at risk of accelerated decline after progression, this does not mean that they cannot safely enjoy an intermittent strategy including periods off chemotherapy when treatment has not yet failed. Thus such patients with disease control can be appropriately counselled about the safety of chemotherapy free intervals.

These data allow the development of two non-mutually exclusive hypotheses to explain the inferior survival of *BRAF*-mutant patients. Firstly these patients may simply have a worse prognosis from initiation of their treatment programme and their equivalent PFS and DCR reflects enhanced relative benefit from first-line chemotherapy, particularly with oxaliplatin, in comparison with wild-type patients. Alternatively the poor survival may be driven by mechanisms mediating first-line chemotherapy resistance when superimposed on the *BRAF*-mutational landscape. This is supported by markedly worse post-progression survival independent of the delivery of second-line treatment, and the lack of PFS and OS deterioration in *BRAF*-mutant patients stable on first-line Ox/FP receiving chemotherapy-free breaks.

Disappointing results of *BRAF*-inhibitors as single agents in aCRC[25] and a growing appreciation of the molecular complexity of *BRAF*-mut aCRC[26] suggest that targeted approaches may require multi-agent combinations. Early clinical studies report encouraging clinical activity and acceptable toxicity with the combination of a *BRAF*-inhibitor, a MEK inhibitor and an anti-EGFR agent.[27] These regimens are complex and likely to be expensive and will complement rather than replace chemotherapy.

This, the largest and most comprehensive analysis of chemotherapy outcomes in *BRAF*-mutant CRC patients provides new and important information with clinical relevance. In summary, *BRAF*-mutation confers a markedly worse prognosis independent of associated clinicopathological features. However chemotherapy does provide meaningful improvements in outcome throughout treatment lines. Post-progression survival is markedly worse and vigilance is required to ensure the appropriate delivery of treatment after first-line progression.

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COMPETING INTERESTS

No authors have declared no conflicts of interest

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Legend to Figures

Figure 1- Consort diagram of study participants from the FOCUS, COIN and PICCOLO trials

Figure 2 –OS KM curves for *BRAF*-mut vs *BRAF*-wt for first line chemotherapy (FOCUS and COIN, all strategies)

Figure 3 - Post-progression survival KM curves for *BRAF*-mut vs *BRAF*-wt following failure on first-line chemotherapy (COIN and FOCUS)

Figure 4 – Forest plot of OS and PFS for first-line intermittent vs continuous chemotherapy by BRAF-status