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Spend less to achieve more: Economic analysis of intermittent versus continuous cetuximab in KRAS wild-type patients with metastatic colorectal cancer

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ABSTRACT

Background: In 2014, the COIN-B clinical trial demonstrated that intermittent cetuximab (IC) was a safe alternative to continuous cetuximab (CC), with less cytotoxic chemotherapy, in first-line treatment for *KRAS* wild-type metastatic colorectal cancer (mCRC). Cetuximab has been available for this indication in England since 2015, but treatment breaks beyond 6 weeks were prohibited, despite real-world evidence that therapy de-escalation maintains equivalent disease control, but with superior Quality-of-Life (QoL). We performed health economic analyses of IC versus CC and used this evidence to help underpin policy change and guide clinical practice through reduction in unnecessary treatment for mCRC patients.

Methods: Employing cost-minimization analysis, we conducted partitioned survival modelling (PSM) and Markov Chain Monte-Carlo (MCMC) simulation to determine costs and quality-adjusted-life-years for IC versus CC.

Results: IC reduced costs by £ 35,763 (PSM; $p < 0.001$) or £ 30,189 (MCMC) per patient annually, while preserving treatment efficacy and enhancing QoL. Extrapolating to all mCRC patients eligible for cetuximab therapy would have generated cost savings of ~£ 1.2 billion over this cohort's lifetime. These data helped underpin a request to NHS England to remove treatment break restrictions in first-line mCRC therapy, which has been adopted as an interim treatment option policy in colorectal cancer during the Covid-19 pandemic.

Conclusions: Our results highlight substantial cost savings achievable by treatment de-escalation, while also reinforcing the importance of therapy breaks to potentially increase tumour responsiveness and reduce treatment toxicity. Our study also highlights how health economic evidence can influence health policy, championing reduced treatment intensity approaches without compromising patient outcomes, which is of particular relevance when addressing the reduced capacity and treatment backlogs experienced during the pandemic.

1. Background

Colorectal cancer (CRC) is a significant health challenge in the UK, with 268,568 individuals living with CRC [1], 16,261 deaths [2] in 2013, and around 43,000 newly diagnosed cases per year [3]. That year, CRC cost the NHS £ 412 million (M) which, when added to societal costs

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due to mortality, morbidity, and informal care, brings the total economic burden of CRC in the UK to £ 2billion (B) [4]. Currently, 25 % of CRC patients in the UK have metastatic CRC (mCRC) at diagnosis [5], while another 25 % develop metastatic disease following earlier stage at diagnosis. Although overall survival (OS) has doubled to ~30 months in the last 20 years [6], the 5-year survival for stage IV CRC is only 7.5 % [7], indicating the need to improve patient treatment options for this aggressive disease.

Cetuximab is a monoclonal antibody (MoAb) targeting the epidermal growth factor receptor (EGFR) signalling pathway that is frequently dysregulated in CRC. Cetuximab was initially approved in 2007 as a mCRC-targeted therapy by the National Institute for Health and Care Excellence (NICE), though it was later found to be ineffective against mCRC patients carrying the mutated form of the Kirsten rat sarcoma (KRAS) gene, which occurs in ~40 % of CRC patients [8,9]. Cetuximab can be used as a single agent [10] or more commonly with chemotherapy combinations such as FOLFOX (FOL– Folinic acid F – Fluorouracil OX– Oxaliplatin) or FOLFIRI (FOL– Folinic acid F – Fluorouracil IRI – Irinotecan). As a monotherapy, cetuximab's toxicity profile is lower, but clinical benefit is greater when used in combination with chemotherapy in first line [11].

In mCRC patients for whom cetuximab is effective, therapy will inevitably apply a selection pressure, leading to emergence of treatment-resistant cell populations [12]. One potential way of subverting this resistance is by employing an adaptive "stop-go" treatment strategy, whereby patients are allowed treatment holidays or breaks until tumour regrowth, when therapy is reinitiated [13]. The alternative is to continue antibody treatment relentlessly until treatment failure is demonstrated. An individual patient meta-analysis of studies evaluating treatment breaks in mCRC has established that treatment break strategies do not negatively impact OS when compared to continuous therapy [14]. A major contributing study to that individual patient data meta-analysis (IPDMA) was the COIN (COntinuous or INtermittent) trial, which marginally failed to confirm non-inferiority of intermittent therapy (HR 1·087 (80 % CI 0.986–1·198; 95 % CI 0.936–1·261)), but bearing in mind the reduction in toxicity and quality of life improvement, established that intermittent chemotherapy was a viable treatment option for patients with mCRC, with minimal effect on OS [15]. COIN-B was a (phase II) extension of this trial, demonstrating that intermittent cetuximab (IC) could be safely incorporated into this treatment regimen [16].

The COIN (COntinuous or INtermittent) trial established that intermittent chemotherapy was a viable treatment option for patients with mCRC, resulting in enhanced QoL compared to continuous therapy, but with minimal effect on OS [15]. COIN-B was a (phase II) extension of this trial, demonstrating that intermittent cetuximab (IC) could be safely incorporated into this treatment regimen [16]. As a lower use of cetuximab and chemotherapy could reduce costs and given that the IC arm had equivalent clinical efficacy but potential for better Qol to the continuous cetuximab (CC) arm, we employed cost-minimization analysis (CMA) [17] to determine which intervention was the least costly and delivered better value, both for patients and health systems. Whilst we have become accustomed to cost-versus-efficacy analyses for the introduction of new drugs on a global level, we have failed to fully explore the adaptation of strategies using these drugs which may demonstrate equivalent efficacy at lower cost. Notably, when many countries around the world now adopt a threshold-to-pay based upon societal perceptions within the individual country, such strategy-based adaptations may have a significant impact upon willingness-to-pay for effective therapies. Within the setting of advanced CRC, the use of intermittent therapy strategies for drugs initially licensed based upon continuation to progressive disease (or even beyond in the case of bevacizumab) has been explored in a large number of academically-led phase II and III RCTs. These trials have shown no survival benefit for a continuation-of-therapy strategy versus a stop-and-start strategy and have indicated lower toxicity with improved QoL in those who are able to receive the stop-and-start treatment. The EGFR inhibitors cetuximab and panitumumab are the most expensive systemic therapies used in the first line setting of the majority of patients with advanced CRC and so cost-effective strategies for the use of these drugs has potential to reduce toxicities, improve QoL and thus reduce cost per QALYs, increasing likelihood-to-pay thresholds.

We appraised the costs not only of chemotherapy and cetuximab treatment, but also drug administration, associated patient care, and costs incurred due to toxicities from adverse events. To our knowledge, this is the first formal economic analysis of intermittent dosing of cetuximab in a clinical trial setting and has significant implications for patients' QoL, whilst also capturing information on healthcare expenditure that can inform cancer policy.

2. Methods

2.1. Overview

CMA was performed by examining the healthcare costs (y-axis) and health outcomes (x-axis) visually on the cost-effectiveness plane. The resulting scatterplot was measured against a cost-effectiveness threshold or willingness-to-pay (WTP), the latter is the maximum amount a consumer (or society) will forgo to purchase a product. Following NICE guidelines, CMA was expressed in UK pounds sterling at 2013 prices (the most recent year at the time of analysis that there was a complete audit with data available for CRC patients in the UK). Quality-adjusted life-years (QALYs) were used as a measure of health outcomes, with both future costs and outcomes discounted at 3.5 % per annum. We employed both partitioned survival modelling (PSM) and Markov Chain Monte Carlo (MCMC) simulation to ensure a robust health economic analysis.

2.2. Study population

COIN-B was an open-label explorative phase 2 trial, with a total of 164 patients randomised to receive either continuous cetuximab (CC) (N = 88 patients) or intermittent cetuximab (IC) (N = 76 patients) therapy; all were treated with the same intermittent chemotherapy. All patients were aged 18 years or over with mCRC, had not received any previous chemotherapy for advanced disease, and were enrolled in 30 UK hospitals and one in Cyprus. The trial was initially implemented before it was known that patients with *KRAS* mutations do not benefit from cetuximab;[10] once this knowledge became available, the trial was temporarily suspended and then adapted to only include $KRAS^{wt}$ patients.

2.3. Health utility, resource use and cost assessments

Health utility scores were derived from the COIN trial, which employed the EQ-5D-3 L questionnaire. Medical resources for each patient group (such as pharmaceutical costs and patient care) were based on their utilisation in the COIN-B trial, with costing data obtained from NICE. Chemotherapy, cetuximab, and patient care costs were calculated on a weekly basis and multiplied to match the treatment regimen for each patient. Toxicity data for Grade 3/4 (serious) adverse events and their associated costs were derived from COIN-B trial and National Reference Costs from the NHS, respectively. All utilities and costs, together with patient data, were used to populate both the PSM and MCMC simulation, and are listed in Supplementary Materials (Supplementary Tables S1-S4).

2.4. Partitioned survival modelling (PSM)

PSM is an economic framework used to model a cohort over their lifetime as they move between a set of exhaustive and mutually exclusive heath states such as PFS and post-progression survival (PPS). It differs from a Markov model in that it is not determined by transition

probabilities. Rather, the model approximates the fraction of the cohort in each state derived from parametric survival equations. Combining data from Kaplan-Meier survival curves in the COIN-B clinical trial for OS and PFS, the time in PPS was calculated by subtracting PFS from OS (Fig. 1). For each patient, QALYs were calculated by multiplying the utility score (derived from time spent in PFS and PPS) by life-years gained. Weekly costs of pharmaceutical administration and associated patient care were calculated and multiplied by the number of life-weeks gained for each patient. Patients who experienced therapy-related toxicities had their adverse event management costs added to overall treatment costs, with discounting applied to the final figure. Final costs and QALYs were presented in Stata (StataCorp. 2015. Stata Statistical Software: Release 14.2. College Station, TX: StataCorp LP) and ordinary least squares (OLS) regression performed on costs and QALYs separately, based on whether they originated from CC or IC treatment. Cost/QALY pairs were then determined for each treatment scenario and differences between the two treatments were calculated. This sample was resampled 1000 times (a six-fold increase on the original sample) by bootstrapping, in order to generate a PSM.

The incremental cost-effectiveness ratio (ICER) was calculated as follows:

$$ICER = \frac{C_i - C_s}{E_i - E_s}$$

whereC_i = costs of the intervention therapy (IC).

C_s = costs of the standard therapy (CC)
E_i = effects of the intervention therapy (IC)
E_s = effects of the standard therapy (CC)

Net monetary benefit (NMB) was calculated by subtracting the difference in costs from the product of the WTP threshold and the difference in QALYs, as follows:

$$NMB = \lambda \times \triangle E - \triangle C$$

where λ = WTP threshold.

Δ E = difference in effects

Δ C = difference in costs

This analysis was performed for each cost/QALY pair for WTP thresholds between £ 0 and £ 50,000. The resulting NMB sum of 1000 samples for each λ bin was calculated and the average taken. Corresponding confidence intervals (CIs) were calculated. The probability that IC therapy was cost-effective over CC therapy was calculated for a range of WTP values between £ 0 and £ 125,000 and mapped on a cost-effective acceptability curve (CEAC). The value of information (VOI) to treat, employing IC therapy rather than CC therapy was calculated for WTP values between £ 0 and £ 150,000.

2.5. Markov Chain Monte Carlo (MCMC) simulation

Each patient in the trial had outcomes of OS and PFS, with particular attention to the three states of PFS, PPS, and death and the transitions within. Transition probabilities between the different health states (PFS, PPS and death) were calculated by extracting survival data (OS & PFS) at 6-month intervals from the COIN-B trial. PPS was calculated by subtracting PFS from OS as in PSM, but in preparation for the MCMC simulation, raw cohort data was transformed into 6 monthly event rates, using the formula:

$$r = \ln(1 - p) \quad (1)$$

where p is the probability of remaining in a specified health state. This rate r is converted into a weekly rate and transformed back to a weekly transition probability. Transition probabilities were used to populate the transition matrices (Tables S1.1 and S1.2 - Supplementary Materials). Weekly transition probabilities were employed due to the aggressive nature of mCRC and the dynamic occurrence of associated toxicities from drug administration.

In the MCMC simulation, transition probabilities were based on the a priori assumptions described above and were fixed, regardless of the cycle number (time elapsed). Thus, the transition probabilities were a snapshot based on the observed aggregate movement of patients from PFS to PPS to death over the first six months, and not based on the individual patient data from every transition in the COIN-B trial, as occurs with PSM [18].

MCMC comprises two parts: (i) the Markov chain, which in this case

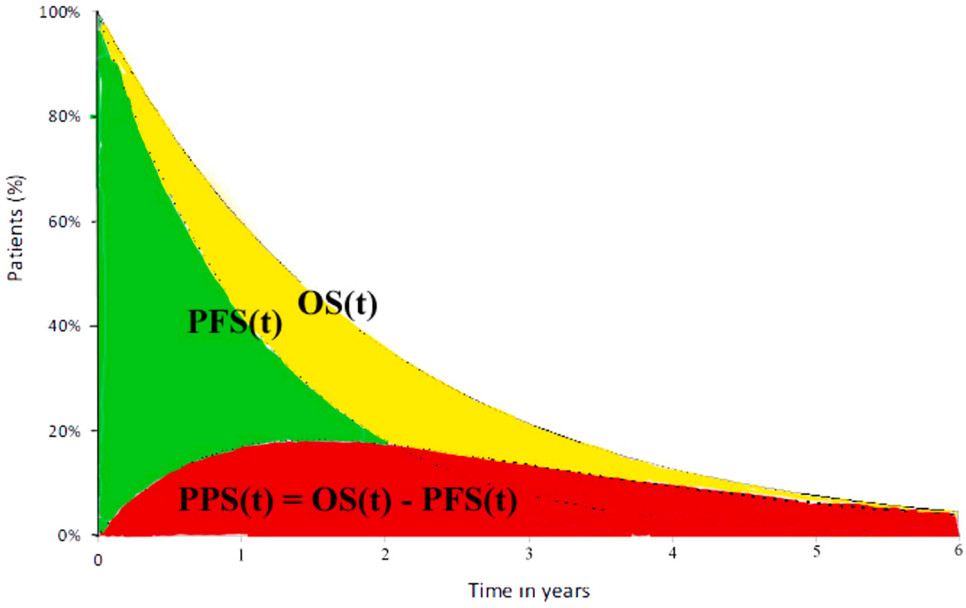

Fig. 1. Schematic determining state membership in PSM models, an example of a three-state cancer model. PPS(t) denotes progression state as a function of time (t). OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.
(adapted from Woods et al.)[41]

comprises three health states, with arrows showing the permitted probability transitions (Fig. 2). (ii) Monte Carlo sampling from the probability distribution created by the Markov chain.

The Markov chain is a simple 3-state model represented schematically (Fig. 2) and populated by the transition probability matrices (Tables S1.1 and S1.2). Initial probabilities for each state were set at 1 for PFS, and 0 for PPS and dead. These initial probabilities were multiplied by the transition probability matrix.

This 'Markov trace' continued in discrete weekly cycles for a time horizon of 6 years (when all patients had died). The products of these probabilities were used to calculate corresponding costs and outcomes (QALYs), where future costs and QALYs are discounted, and a half-cycle correction applied (costs and QALYs are known at the beginning and end of each week but not the mid-point). Distributions of costs and QALYs generated from the Markov trace (the range of probabilities in the 3 states from Week 1 to Week 312) were sampled iteratively and randomly by a Monte Carlo simulation, producing a probabilistic sensitivity analysis (PSA).

The ICER was calculated as outlined in the PSM, as was the NMB, but only for a WTP of £ 30,000 and no CIs were generated. CEAC was also plotted from the MCMC simulation for WTP values between £ 0 and £ 100,000. VOI was not calculated for the MCMC simulation.

2.6. Cost savings in 2013 cohort

The formula below was used to calculate cost savings in the 2013 cohort.

$$\begin{aligned} &Cost\ \ saving\ \ per\ \ patient\ \ (CC\ \ therapy - IC\ \ therapy) \\ &\times no.\ \ of\ \ CRC\ \ patients \times mCRC\ \ proportion \\ &\times RAS\&BRAF\ \ WT\ \ proportion \times leftsided\ \ proportion \\ &\times IC\ \ fit\ \ proportion \\ &= cost\ \ savings\ \ produced \end{aligned}$$

2.7. Comparison of survival curves with markov trace

The combined Kaplan-Meier survival curves from COIN-B were compared to the Markov trace generated from the transition probabilities from the first 6 months of the trial. Survival curves from both models were plotted for IC therapy only.

2.8. Patient and Public Involvement (PPI)

COIN-B trial was developed/delivered in collaboration with PPI representatives from the COIN Treatment Management Group. Additionally, focus groups were held with patients and relatives regarding the pros and cons of intermittent therapy, which informed the positive and negative aspects of an interval off therapy from the patient perspective. PPI representatives were involved in the oversight groups in the MRC trial steering committee and were consulted about the burden of the study participation.

Bowel Cancer UK (BCUK), our patient organization partner, have been involved from the start of the health economic study and led the submission to the NHS England Chemotherapy CRG. Input from BCUK and their patient group fed into the research aims and BCUK were a member of the design team for the study. BCUK were also represented on the study writing group. BCUK patient group members provided case studies to inform the NHS England submission.

Study results will be disseminated with appropriately patient-adapted language through BCUK and through the NCRI Consumers Forum for both patients and the wider public.

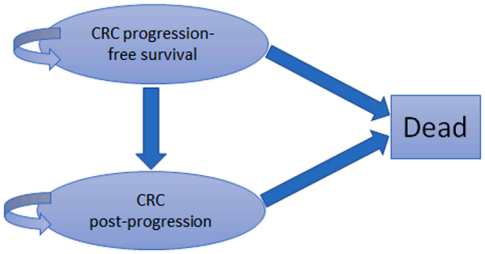

Fig. 2. Markov Model. CRC, colorectal cancer.

3. Results

There were 164 patients ($KRAS^{wt}$ status) in this analysis, with 88 receiving CC therapy and 76 receiving IC therapy. Comparing mean differences in QALY data between CC and IC therapy gave a *t*-test score of − 0.0314, consistent with the hypothesis that the two approaches have similar clinical effect (H_a; $p > 0.975$). The first death was recorded at 20 days and the last death at 6.21 years.

3.1. PSM and MCMC simulation on cost-effectiveness plane

Our results for PSM ICER were as follows:

$$ICER = \frac{£70,168 - £105,931}{1.2573 - 1.2465} = \frac{-£35,763}{0.0108} = ICER\ \ not\ \ reported$$

PSM indicates that there is a strong linear relationship between costs and QALYs (Supplementary Fig. S1). Costs were higher and rose more steeply for the CC cohort (£79,967 to £138,650, average = £109,308) than the IC cohort (£55,589 to £84,597, average = £70,093), the range in QALYs was 0.94–1.64 (average = 1.29) for the CC cohort and 0.97–1.56 (average = 1.27) for the IC cohort. There was an incremental cost saving per patient of £ 35,763 (p-value < 0.001) in favour of IC.

The vast majority of the difference in costs and QALYs between CC and IC therapies are below both WTP thresholds of £ 30,000 (99.6 % below green line) and £ 50,000 (98.3 % below red line) (Fig. 3), falling into the South-West or South-East (IC therapy dominates) quadrants of the cost-effectiveness plane.

Results for MCMC simulation ICER were as follows:

$$ICER = \frac{£53,334 - £83,523}{1.1255 - 1.2297} = \frac{-£30,189}{-0.1042} = ICER\ \ not\ \ reported$$

MCMC simulation cost/QALY pairs (Supplementary Fig. S2) indicate that costs for the CC cohort (£76,923 to £234,480, average = £83,524) were higher and had a wider range than the IC cohort (£55,975 to £136,530, average = £56,489). QALYs ranged from 1.06 to 1.36 (average = 1.24) in the CC cohort to 0.97–1.25 (average = 1.13) in the IC cohort, that is a similar spread, but CC therapy produces slightly more QALYs. There was an incremental cost saving per patient of £ 30,189 in favour of IC therapy.

In the MCMC simulation, the great majority of the difference in costs and QALYs between CC and IC therapies are below WTP thresholds of £ 30,000 (97 % below the green line) and £ 50,000 (96.5 % below the red line), with IC therapy dominating (Fig. 4).

3.2. Net monetary benefit

For PSM, Fig. S3 (Supplementary), shows the NMB was greater than zero for all WTP threshold values between £ 0 and £ 50,000; additionally, at a WTP of £ 30,000, IC therapy was £ 35,349 less expensive than CC therapy ($p < 0.008$) and at a WTP of £ 50,000, IC therapy was £ 35,223 less expensive than CC therapy ($p < 0.034$). The NMB for the MCMC simulation was £ 19,768.

3.3. Cost-effective acceptability curve

The CEAC for the PSM compared IC therapy to CC therapy over a

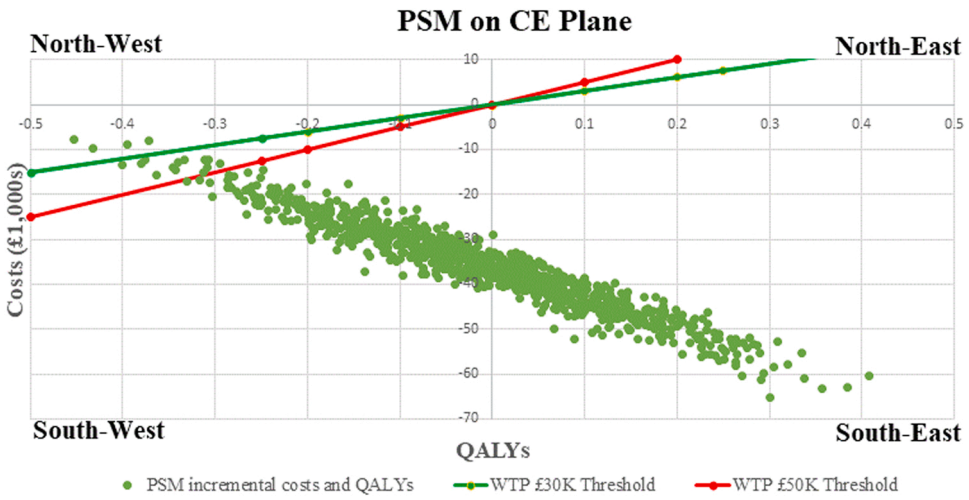

Fig. 3. Partitioned Survival Model – incremental costs and QALYs on the cost-effectiveness plane. CE, cost-effectiveness; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

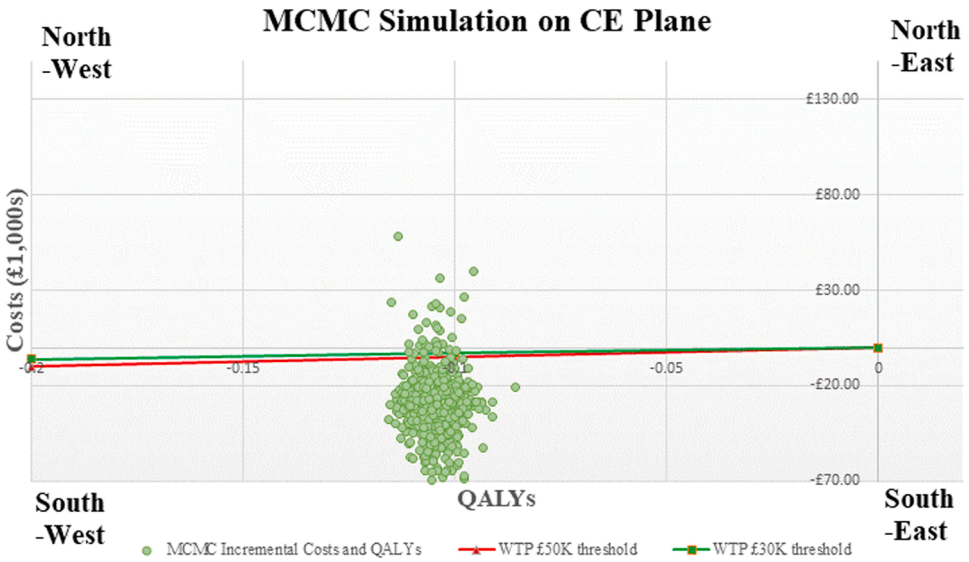

Fig. 4. Markov Chain Monte Carlo simulation - incremental costs and QALYs on the cost-effectiveness plane. CE, cost-effectiveness; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

range of WTP values and found the probability of IC therapy being the more cost-effective option from 100 % at £ 782 ($p < 0.001$) to 98.3 % at £ 50,000 ($p < 0.034$), the results become statistically insignificant between £ 57,578 ($p < 0.046$) and £ 68,457 ($p > 0.060$) (Supplementary, Fig. S4). The CEAC for the MCMC simulation found the probability of IC therapy to be the most cost-effective option 100 % of the time over CC therapy for a range of WTP values from £ 0 to £ 100,000.

The VOI curve was constructed from PSM results only (Supplementary, Fig. S5); VOI increases with a range of WTP values (from £0 to £150,000), however as the data indicate a high certainty that IC therapy should be adopted as an alternative to CC therapy (only 4 out of 1000 simulations for IC therapy were not cost-effective), there is a very small VOI (£16) of reducing uncertainty at a WTP of £ 30,000 and a VOI of £ 97 at a WTP of £ 50,000. VOI analysis would indicate that as WTP grows, it would be too costly to remove all decision uncertainty and achieve the perfect information that IC therapy is more cost-effective than CC therapy.

3.4. Cost savings in 2013 cohort

Of the 268,568 CRC patients identified in the UK in 2013 [1], approximately half will develop mCRC [19], 44 % of whom are wild-type for *RAS* and *BRAF*, thereby qualifying for cetuximab therapy [20]. Tumour sidedness of mCRC is also predictive of response to cetuximab, with 78 % of wild-type patients with left-sided tumours having superior outcomes [21]. Additionally, findings from COIN-B suggest that only 70 % of this left-sided, wild-type cohort will be eligible for IC therapy due to their comorbidities [16]. Thus, the cost savings of adopting IC therapy over CC therapy were assessed for these eligible 2013 mCRC patients: using PSM, cost savings of IC therapy were £ 35,763/year per patient ($p < 0.001$) as indicated above. If IC therapy was employed over CC therapy in the 2013 cohort, we estimate lifetime savings for these patients to be £ 1153,728,262.

3.5. Comparison of survival curves with markov trace

PSM is drawn directly from clinical trial data whereas the Markov trace is based on fixed transition probabilities from the first 6 months

survival in the trial. PSM and Markov trace survival curves for IC therapy were compared (Fig. 5). After Year 1, the Markov trace underestimates the OS (PSM 65.8 % vs Markov 59.8 %) and PPS curve (PSM 44.7 % vs Markov 21.6 %) compared to PSM, but overestimates PFS curve (PSM 21.1 % vs Markov 38.2 %) compared to PSM; this was even more pronounced by Year 2 (Supplementary Table S5). Thus, PSM represents a more accurate portrayal of clinical trial data than Markov modelling and should be the preferred methodology for analyses of this type. (Table 1).

4. Discussion

Treatment paradigms in metastatic colorectal cancer have evolved significantly over the last decade, in particular with the introduction of immunotherapy for MSI-H cancers and combination targeted therapy for BRAF mutated cancers. For patients with *KRAS*^{wt} (and latterly all-RAS^{wt}), individualised treatment approaches using MoAb-based therapies including cetuximab or panitumumab directed against EGFR in mCRC patients have defined a new standard-of-care [22]. As our clinical experience of these targeted agents in combination with chemotherapy evolves, there is increasing evidence that treatment breaks or "holidays" may deliver QoL benefits for mCRC patients, reduce hospital attendances and in-patients stays and have biological relevance in the continuum of CRC care, while potentially achieving substantial financial savings for healthcare systems. Disease progression due to drug-selected expansion of resistant *KRAS*^{mut} clones is invariable, but treatment breaks from anti-EGFR therapy provide a potential window of opportunity, fostering a re-emergence of *KRAS*^{wt} clones that remain sensitive to re-challenge with EGFR MoAb. Furthermore, treatment breaks provide the opportunity to test the tumour's *KRAS*^{wt} /*KRAS*^{mut} ratio by liquid biopsy, informing precise management of both timing and duration of re-challenge [23].

Current regimens and treatment sequencing have increased median OS in mCRC to 30 months; however, patients are now exposed to chemotherapy for longer periods of time than before. Real word data indicate that treatment de-escalation is relatively common, with almost a third of patients receiving intermittent chemotherapy as a viable approach [24]. In this scenario, clinicians make informed decisions which they believe are in the patients' interest. Treatment breaks may thus reduce potential side-effects associated with continuous therapy and contribute to improved QoL [15]. Employing an intermittent therapeutic approach may also help reduce costs when compared to continuous therapy; however, health economic comparisons of this type of approach are rarely reported [25].

In this study, we report, for the first time in a RCT setting, a Cost Minimisation Analysis (CMA) comparing intermittent cetuximab (IC) versus continuous cetuximab (CC) costs in patients enrolled in COIN-B, a non-inferiority trial which indicated the potential for IC to have equivalent clinical efficacy to CC in mCRC. Both Partition Survival Modelling (PSM) and Markov Chain Monte Carlo (MCMC) Simulation results evidence this clinical equivalence, with minimal differences between the therapies (PSM = +0.01 QALYs, MCMC = −0.1 QALYs), but with significant cost reduction per patient for IC therapy. PSM results are distributed more over costs, and MCMC Simulation is distributed to a lesser extent over QALYs. These minimal variances are likely due to the 'smoothing' of clinical trial data by MCMC. Net Monetary Benefit (NMB) analysis indicated that IC had a superior value over CC.

Table 1
Matrix multiplication of initial probabilities by transition probability matrix for IC in the first week cycle. PFS, progression-free survival; PPS, post-progression survival.

				Transition Probability Matrix			
				Transition from:	Transition to:		
Initial Probabilities					PFS	PPS	Dead
PFS	PPS	Dead		PFS	0.982	0.012	0.006
1	0	0	x	PPS	0	0.976	0.024
				Dead	0	0	1

We extrapolated our results to the eligible UK *KRAS*^{wt} population in 2013 who were expected to develop mCRC. If IC therapy had been adopted over CC therapy, we estimate a cost-saving of almost £ 1.2 billion from our PSM model. If implemented, further substantial societal savings for IC therapy are likely, since this approach requires fewer visits to hospital clinics and thus reduction in travel costs and time off work for patients.

Strengths of this study include the fact that the primary analysis was performed by a multidisciplinary independent research team (DFr, ML, and RH), which liaised with the original COIN/COIN-B clinical team. This negated bias and underpinned independent health economic analysis. PSM and MCMC simulation were comprehensively evaluated, with coding thoroughly checked and robustness of models tested. Results were validated by comparing to a UK economic model [26], which found cetuximab plus irinotecan therapy to be £ 88 K per QALY, similar to our MCMC simulation result of £ 83.5 K for CC therapy.

An important limitation relates to the trials themselves. The COIN study did not formally demonstrate the non-inferiority of an intermittent versus continuous chemotherapy regimen. The COIN-B study compared intermittent chemotherapy with continuous cetuximab versus intermittent chemotherapy with intermittent cetuximab. Additionally, models have their weaknesses and a limitation of this study is its sample size. COIN-B was a phase 2 trial, and as such had a smaller sample size ($N = 164$) than a phase 3 trial and was not powered to demonstrate non-inferiority in terms of overall survival. In spite of these limitations however, the CEAC demonstrated that IC therapy had greater value for money over CC therapy, emphasising the need to deploy this type of analysis and have access to this type of data to inform current clinical

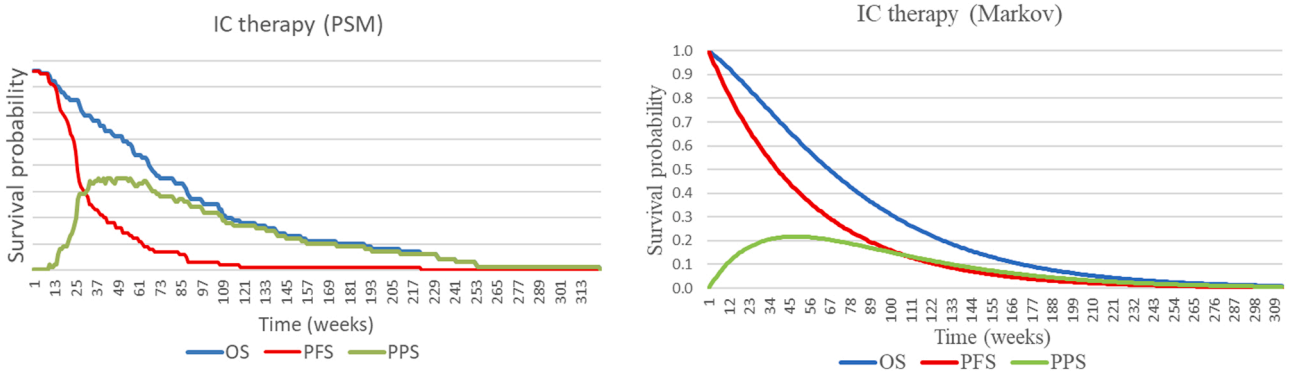

Fig. 5. Comparison of PSM survival curves and Markov trace for IC therapy. IC, intermittent cetuximab; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

practice planning, together with the importance of funding academically-led research in the post-licensing setting to explore efficient, but also effective strategies for the use of novel therapies.

Recently, two additional phase II studies [27,28] have been published which attempt to address the use of EGFR monoclonal antibodies as a maintenance strategy. These provide additional data to explore this question, but we do not see that these studies either change or challenge our overall conclusions. Valentino [27] explored the use of panitumumab maintenance versus panitumumab and 5-Fluorouracil, whilst Panama [28] investigated the use of 5-FU versus 5-FU plus panitumumab. These studies suggest that more active therapies in the interval can result in a prolongation of PFS, prior to a return to induction therapy. However, we question whether the approach of 'more is better' for the patient using our current therapies will enable us to reach the bar of enhancing quality of life with the same survival benefit. These two-phase II studies both evidence our caution further, with the Valentino study demonstrating no OS benefit but a more than doubling of G3–4 toxicities from 20 % to 42 %. The Panama study also demonstrating no OS benefit with G3–4 toxicities increasing from 26 % to 43 % with the doublet versus single agent approach. Some patients and their clinicians will find these toxicities acceptable, but many others will not; this is reflected across the trials, with a reduction in patients in the more intense arms recommencing full dose induction therapy upon progression.

The intermittent treatment approach that we have evaluated was initially described in the Medical Research Council's (MRC) CR06 trial [29], which evaluated treatment breaks in mCRC in the absence of tumour progression. Since then, numerous clinical trials have applied a stop-and-go approach in this setting [30]. De-escalation/re-escalation of oxaliplatin administration, the most toxic drug of the FOLFOX/cetuximab regimen, had a major impact on OS, when re-introduced after a treatment break [31]. Retaining 5-FU with panitumumab rather than panitumumab alone in partial stop-and-go approach may increase OS, while reducing drug costs [32]. Phase 3 studies of bevacizumab (CAIRO [33], AIO0207 [34] studies) similarly show no OS advantage of continuous versus intermittent approaches. Critically, a meta-analysis of individual patient data from over 4000 patients receiving intermittent versus continuous chemotherapy (+/- anti-EGFR MoAb) indicated equivalent OS [35]. Where an intermittent therapy strategy was adopted, including a complete break, the period of time off therapy without detrimental impact was substantial, thus providing meaningful QoL benefit for a large subset of patients. Notably, patients who adopted an intermittent strategy had on average 2.3 months less time on chemotherapy [35].

In studies which evaluated QoL, there were significant benefits from intermittent therapy in relation to fatigue, dry/sore mouth, eating/drinking problems, difficulty handling small objects, interference with daily activities, nausea or vomiting, appetite loss, constipation, and diarrhoea. Intermittent therapy also had significant benefits for role/social functioning. Toxicities specific to continuous EGFR MoAb administration included significant low grade and ≥G3 skin rash, lethargy, stomatitis, peripheral neuropathy and diarrhoea; these were reduced in the IC setting [35]. A systematic review and network meta-analysis of randomised clinical trials in mCRC indicated that treatment breaks should be considered [35]. The highest levels of evidence from an IPDMA including 9 trials and a total of 4178 patients indicate no detriment in overall survival (HR = 1.03 [95 % CI 0.93–1.14]), for patients receiving an intermittent therapy strategy, whether from complete break (HR 1.04 [95 % CI 0.87–1.26]) or maintenance strategies (HR 0.99 [95 % CI 0.87–1.13]) [14].

The previous NHS England treatment breaks policy for cetuximab and panitumumab in mCRC specified that planned breaks from treatment longer than six weeks are not permitted [36] and crucially funding for treatment is then no longer guaranteed. This policy is not beneficial for patients, many of whom are forced to stay on continuous therapy despite their concern about potential side effects, as they are more worried about the risk of their treatment not being funded following a treatment break. In November 2019, the authors of this paper in collaboration with the cancer charity Bowel Cancer UK provided a significant body of evidence including medical evidence and the health economic analysis presented here, along with a series of patient case studies, to challenge this treatment break policy [36]. The submission was considered by the NHS England Chemotherapy Clinical Reference Group (CRG). Having reviewed the evidence, they agreed that a change in the treatment break policy for cetuximab and panitumumab should be considered, although the timeline was unclear. The advent of Covid-19 and its impact on cancer systems has made the consideration of treatment breaks even more relevant, given the delays that have been experienced in delivering treatment [37] and the inevitable diagnostic and therapeutic backlogs [38,39]. In this setting, the inclusion by NHS England (latest update 1st April 2022) of advice on interim treatments permissible during the Covid-19 pandemic has been encouraging. They highlight the option to give intermittent treatment with chemotherapy regimens that contain cetuximab or panitumumab, in order to reduce the need for immunosuppressive treatment in CRC;[40] This is an extremely encouraging response to our combined efforts with BCUK to deploy health economic and other relevant data to inform cancer policy.

In conclusion, the evidence provided by our robust health economic analysis has been instrumental in influencing a policy change that reduces unnecessary cancer treatment for cancer patients; this has particular resonance during the Covid-19 pandemic and can benefit both the individual CRC patient and also the National Health System. We recommend that formal health economic analysis should be considered as part of the evidence base to support adjustment in treatment approaches for cancer patients that make the best use of available resources, while ensuring the optimal treatment intervention that gives the best outcomes and enhances quality of life for cancer patients.

Authors contributions

R.H.H. had full access to all the data in the study and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, and attests that all authors meet authorship criteria and that no others meeting the criteria have been omitted. Concept and design: R.H.H., M.L., D.Fr. Acquisition, analysis, or interpretation of data and validation of Model: R.H.H., M.L., D.Fr. Drafting of the manuscript: R.H.H., M.L., D.Fr. Critical revision of the manuscript for important intellectual content: E.M.F., R.A., H.W., R.G.J., D.Fi., S.R., P. D., L.W., T.M., R.S. Obtained funding: M.L., T.M. Administrative, technical, or material support: D.Fi., P.D.

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Trial governance

COIN-B (ISRCTN38375681) was designed by the COIN TMG. It was approved by the South West Research Ethics Committees and the Medicines and Healthcare Regulatory Agency (MHRA) in the UK and the National Bioethics Committee and the Pharmaceutical Services of the Ministry of Health in Cyprus. The MRC was the sponsor. The trial was conducted by the MRC Clinical Trials Unit (CTU) overseen by an Independent Trial Steering Committee following the principles of Good Clinical Research Practice. Data collection at UK sites was supported by the National Cancer Research Networks.

Competing interests

R.H.H. is employed by a Health Economics consultancy Salutem Insights Ltd. ML is in receipt of honoraria from Bayer, Carnall Farrar, EMD Serono, Novartis, Pfizer and Roche unrelated to this work. ML received an unrestricted educational grant from Pfizer unrelated to this work There are no other conflicts of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jcpo.2022.100342.

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