Title Page

Title:

Treatment breaks in first line treatment of advanced colorectal cancer: an individual patient data meta-analysis.

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Running head:

Review of intermittent therapy strategies on survival in advanced colorectal cancer and the effect of thrombocytosis on efficacy of therapy breaks

Key Points:

1. Survival in advanced colorectal cancer is not affected by the use of an intermittent systemic anti-cancer therapy strategy, whether that be a complete break from therapy or use of a maintenance therapy, when compared with a continuous therapy strategy.
2. Thrombocytosis is a poor prognostic factor in advanced colorectal cancer occurring in around a quarter of all patients. Further, understanding of the role played may lead to future therapeutic strategies
3. Thrombocytosis does not predict for the need for a maintenance or continuous systemic anticancer therapy strategy after 8-24 weeks of induction chemotherapy

Abstract

Background

Intermittent systemic anti-cancer therapy in patients with advanced colorectal cancer (aCRC) may improve quality of life without compromising overall survival (OS). We aimed to use individual patient data meta-analysis (IPDMA) from multiple randomised controlled trials evaluating intermittent strategies to inform clinical practice. We also aimed to validate whether thrombocytosis as a predictive biomarker identified patients with significantly reduced OS receiving a complete treatment break.

Patients and Methods

An IPDMA of intermittent strategy impact on survival was undertaken, including all relevant trials in which data were available. Intermittent strategies were classified into two groups: a planned stopping of *all therapy* ("treatment break strategy"; 6 trials; 2,907 patients) or to the same treatment omitting *oxaliplatin* ("maintenance strategy"; 3 trials; 1,271 patients). The primary analysis sample was of patients successfully completing induction therapy. Additionally, a pre-planned analysis of the predictive value of thrombocytosis on survival under a continuous versus an intermittent strategy was undertaken.

Results

All trials had comparable inclusion criteria. The overall IPDMA of intermittent therapy versus continuous therapy demonstrated no detriment in OS (HR=1.03 [95% CI 0.93-1.14]), 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]). Thrombocytosis was confirmed as a marker of poor prognosis in aCRC, but did not predict for OS detriment from treatment break strategies (interaction HR=0.97 [95% CI 0.66-1.40] compared to continuous therapy).

Conclusion

The highest levels of evidence from this IPMDA indicate no detriment in survival for patients receiving an intermittent therapy strategy, either for maintenance or complete break strategies. Although, thrombocytosis is confirmed as a marker of poor prognosis, it is not predictive of poor outcome for patients treated with intermittent therapy. An intermittent chemotherapy strategy can therefore be applied irrespective of baseline platelet count and does not result in inferior OS compared to continuous chemotherapy.

Article

Background:

Controversy continues regarding the necessity of maintenance therapy in advanced (metastatic) colorectal cancer. Historically, when treatment options were limited, 5FU was continued until disease progression. The introduction of oxaliplatin, with its cumulative neurotoxicity, raised the necessity of interrupting oxaliplatin therapy after a limited exposure to avoid worsening neuropathy. The clinical benefit of continuing systemic anti-cancer therapy is a balance between improved disease control and the reassurance of ongoing therapy on one hand versus ongoing and worsening toxicity and fatigue, repeated hospital visits (including; currently increased risk of exposure to COVID19) and cost, on the other. Conversely, interruptions in chemotherapy offer the benefit of time completely off therapy (away from the hospital), reduced toxicity, and return to 'normal life'; but risk loss of tumour control, earlier onset of tumour-related symptoms and, for some patients, the anxiety of being off therapy.

A number of clinical trials have assessed various strategies for de-escalation of systemic therapy after a period of doublet or triplet treatment. Some of these trials have evaluated a complete stop of systemic therapy until progression, when the initial therapy is restarted. Others have evaluated stopping some elements of first-line therapy whilst continuing with a maintenance strategy, mostly as a "de-escalation" of the initial treatment. Previous meta-analyses (but not IPDMA) of published data have suggested that interruptions to therapy do not result in a deficit in overall survival [1] [2] [3]. A combined analysis of the CAIRO3 and AIO 0207 trials [4] [5] [6] suggested, on the basis of improved progression-free survival, that bevacizumab plus a fluoropyrimidine as maintenance therapy is more beneficial than observation alone and this is widely considered as the current standard of care. Notably, additional analyses in this study demonstrated no significant difference in OS (HR 0.91, 95% CI 0.78-1.05) between the two strategies, and the trials showed marked heterogeneity in overall treatment effect and subgroup effects. Separately, health economic evaluation undertaken by the

CAIRO3 group demonstrated excessive cost implications for the strategy of maintenance therapy with capecitabine and bevacizumab [4] [7].

Most recently Sonbol et al. [8] published a systematic review and network meta-analysis of published data from RCTs assessing the role of maintenance strategies in mCRC. This group identified 12 trials with a total of 5,540 patients, and classified each study arm as either continuous, maintenance or observation. Their network approach confirmed the lack of a clear OS benefit for continuous therapy compared to either maintenance (HR=1.04, 95% CI 0.92-1.17) or to observation (HR=0.95, 95% CI 0.85-1.07), and concluded that shared decision-making should include observation as an acceptable strategy. This review also aimed to rank maintenance strategies of bevacuzimab and/or fluoropyrimidine or capecitabine in terms of efficacy. However, the network approach arguably has the disadvantage that similar strategies are pooled across trials, regardless of a strategy's function within an individual trial protocol. An important unanswered question, therefore, remains as to whether removing some or all treatment in the intermittent phase has a detrimental effect on survival *within the confines of an individual trial protocol*.

The ability to identify those patients for whom an intermittent strategy is safe, and those for whom continuation of therapy is a pre-requisite for improved survival, would greatly aid patient discussions and the decision-making process in those patients who have responding or stable disease whilst receiving first-line therapy. It has been hypothesised that patients with a higher burden of disease or poor prognostic factors might require a continuation-based strategy to prevent disease escape or the development of resistant clones. However, analyses from clinical data have not been able to fully support this concept. The MRC COIN trial [11] compared a strategy of continuous oxaliplatin plus fluoropyrimidine chemotherapy versus a planned complete treatment break in patients with responding or stable disease after 3 months of therapy, with recommencement of the same therapy with any evidence of progression beyond the nadir. Subgroup analysis of this large phase III trial

evaluated sixteen known parameters of clinical and biological poor prognosis, and identified baseline thrombocytosis (platelet count > $400x10^9$/l) as a strong predictive marker of poor survival outcome with a planned intermittent (complete stop) strategy. Conversely, those patients with normal baseline platelet level were found to gain no additional benefit from a continuation strategy, and could safely receive complete treatment breaks with re-initiation of the same therapy upon disease progression. Such patients also demonstrated lower toxicity scores and better quality of life assessments; additional benefits included less overall treatment time, less drug exposure and lower treatment costs.

Thrombocytosis has been identified as a poor prognostic marker in colorectal cancer [14] [15] as well as in multiple other tumour types e.g. cervix [16], renal [17], ovary [18] and lung [19]. Platelets exist in two basic states; activated and non-activated forms. In the activated state, often seen in malignancy, these small but numerous anuclear blood cells are able to secrete sequestered cytokines with known pro-mitogenic potential, including IL-6, VEGF, EGF and PDGF [20]. Simultaneously they increase expression of surface integrins, with increased interaction with their cellular environment. They have the potential to increase angiogenesis and tumour cell migration as well as metastasis formation. It remains uncertain as to whether thrombocytosis is a surrogate marker of a tumour phenotype or whether thrombocytosis is an independent driver regulated by host and stromal components.

The objective of this paper is to investigate the association between treatment strategy and overall survival and also to explore thrombocytosis as a predictive biomarker for strategy optimisation, using individual participant data from all eligible and available randomised trials of intermittent therapy.

Methods:

Identification of eligible studies and patients

Eligible studies were randomised controlled trials in advanced colorectal cancer whose design included at least one pair of randomised arms with the following principal characteristics:

1. an initial *induction phase* of 8 to 24 weeks during which patients on both arms received identical treatment; followed by:
2. an *intermittent phase* during which treatment differed between arms by the removal of one or more (or all) components of therapy.

The regimen used in the induction phase may have commenced either at randomisation or during a pre-randomisation registration period depending on the design of the trial; however, platelet count data must have been collected at the time of commencement of induction therapy (i.e. the baseline). Following the first intermittent phase, eligible trials could allow one or more re-introductions of the initial regimen upon progression (possibly with further intermittent phases), or after a set period of time; or allow no re-introduction at all. Notably, some older studies allowed progression beyond baseline prior to re-introduction of first line therapy but most recommended re-introduction upon progression from the nadir, which is the current recommendation.

A systematic literature review was performed to identify all randomised controlled trials (phase II or III) in advanced colorectal cancer meeting the above criteria. Medline and EMBASE were searched between 1990 and 2020, using the search strategy given in the Online Material. Individual participant data (IPD) concerning treatment allocation, overall survival (OS) and baseline platelet count was sought from all eligible trials.

The collected individual patient data allowed us to undertake a key IPDMA of the impact of intermittent therapy on OS. It also allowed us to explore the impact of platelets as a prognostic marker

in a large number of patients with advanced colorectal cancer and simultaneously allowed us to explore the role of thrombocytosis as a potential predictive marker for planned treatment de-intensification or complete treatment break.

Classification of intermittent strategies

To account for the variation across trials in therapies and strategies used, we mandated that the "control strategy" used in the intermittent phase of a trial must consist either of; the *same* regimen (truly continuous) as used in the induction phase, or a variant with one or more elements dropped. If the latter, then the same elements must also have been dropped in the *comparator* arm, with additional therapies being dropped or all therapies being removed ("treatment break"). For instance, in Table 1 we see that CAIRO3 dropped oxaliplatin from both arms in the intermittent phase (the control strategy is capecitabine plus bevacizumab in this trial, the comparator arm being no therapy). Hence, the control must be either a chemotherapy-based regimen (+/- monoclonal antibody (mAb) and/or oxaliplatin/irinotecan), or mAb alone, and must not contain any therapy element not present in the induction phase.

We then classified the included trials into two subgroups according to their comparator treatment strategy in the intermittent phase (Table 2): firstly, any planned *complete stop* of *all therapy* ("treatment break" schedule) compared to the control schedule; secondly, any planned stop of *oxaliplatin* therapy ("maintenance therapy" schedule) compared to a control schedule with oxaliplatin retained. In the IPDMA, we pooled treatment estimates both within these two subgroups and overall, since it seemed a reasonable hypothesis that between-trial heterogeneity might be at least partly explained by such differences in intermittent strategy.

If more than one arm in a trial was eligible for classification as either the control or the comparator strategy, then we combined those arms in the analysis. For example, in Table 1 we see that AIO 0207 randomised both to Bevacizumab plus fluoropyrimide and to Bevacizumab alone in the intermittent phase; so we combined these arms together to form the control strategy against a "treatment break" strategy.

Primary analysis outcome and sample

The primary outcome was OS. We defined the primary analysis sample as including all randomised patients who successfully completed their period of induction therapy. These are the patients in whom the clinical question is relevant: "should this patient continue chemotherapy, switch to maintenance or have a treatment break?"

In the COIN trial report [11], the interaction between intermittent ("treatment break" strategy) vs continuous chemotherapy and baseline platelet count was reported in terms of a "per protocol" analysis sample, defined *a priori* by the trial team, which sought to include only those patients who completed their initial therapy period and successfully commenced their allocated subsequent strategy (intermittent or continuous). By contrast, in the CAIRO3 [4] and AIO 0207 [5] trials patients were randomised at the end of the induction period, and hence only patients who completed induction therapy were included. In general, data on the exact timing of induction therapy and subsequent strategy was not consistently defined, or available at the individual level, across studies. Hence, the decision was taken to impose a constant time for the initial period, as documented in each trial's protocol, upon all patients; commencing at the start of the induction phase. If a patient had not died, progressed, left the trial or become lost to follow-up after this length of time, they were included in the primary analysis sample. Note that, as a result, sample sizes and results presented here do not necessarily match with results previously published by individual trial teams.

Statistical analysis

Statistical analysis was performed using Stata v16.1, following a pre-specified statistical analysis plan. OS was defined as the time from commencement of the induction phase ("baseline") to death from any cause; survivors were censored at the time of last follow-up. We also defined progression-free survival (PFS) as the time from baseline to first progression or death from any cause; although due to differences in trial design and outcome definition we considered PFS analysis to be exploratory only.

Two-stage meta-analysis methodology was used [21], whereby an unadjusted Cox proportional-hazards model was fitted with a binary indicator variable representing the comparator strategy versus the control strategy, and the resulting effect sizes and standard errors were pooled across trials using the modified Hartung-Knapp-Sidik-Jonkman random-effects model [22], which takes account of the number of different trials available.

For the analyses of thrombocytosis, platelet count at baseline was collected for each individual participant. To provide greater clinical clarity, for the primary analysis this was dichotomised using a cut-point of $400x10^9$/l; a sensitivity analysis of the continuous platelet count data was also performed. The trial-level effect estimates of the interaction between platelet count subgroup (that is, $\leq 400x10^9$/l and $>400x10^9$/l) and continuous vs intermittent therapy were meta-analysed. The same meta-analysis methodology was used as for the main analysis of intermittent vs continuous therapy, but in this case the *interaction* effect sizes and standard errors were pooled [23]. Since the COIN trial provided the original evidence of a possible effect modification with platelet count [11], it was excluded from this analysis in order to validate the effect (Table 2).

Results

Summary and description of available data

The PRISMA flow diagram for this review is shown in Figure 1, and a summary of the eligible trials is given in Table 1. Individual participant data (IPD) concerning treatment allocation, overall survival (OS) and baseline platelet count was successfully collected from nine (53%) of the seventeen eligible trials [11] [5] [9] [4] [13] [10] [25] [12] [26], representing 73% of relevant randomised patients (Table 2). All trials had comparable inclusion and exclusion criteria, and randomised patients equally between arms.

Effect of intermittent versus continuous chemotherapy

We first examine the hypothesis that patients who successfully complete induction therapy, may safely be treated with an intermittent strategy ("treatment break" or "maintenance" schedule), compared to a control schedule, within a specific trial protocol. Figure 2a shows that, in this large dataset (>4,000 patients), the OS curves are almost superimposed; hence there is no evidence to suggest a survival difference between treatment strategies (HR 1.03 [95% CI 0.93-1.14]; Figure 2b). Taking each of the sets of intermittent schedules individually, neither a complete break in therapy (HR 1.04 [95% CI 0.87-1.25], Figure 3a), nor a maintenance strategy omitting oxaliplatin (HR 0.99 [95% CI 0.87-1.13], Figure 3b) show a significant difference in overall survival compared to continuous therapy. There is moderate heterogeneity (I-squared = 46%) within the subgroup of trials which stopped all elements of therapy in the intermittent arm. Supplementary Figure S1 shows that, although prognosis was generally somewhat poorer in the COIN trial (possibly, due to variance in entry criteria, national practice etc.), the relative effect of treatment strategy does not appear to differ from that seen in the remaining trials.

In an exploratory analysis of progression-free survival (PFS), the group of trials with a "treatment break" comparator strategy saw an increase in median PFS from continuous therapy of around 2

months (from 8 to 10 months), with an estimated HR of 1.53 (Supplementary Figure S2a). For the group of trials using a "maintenance" comparator strategy, we observed an increase in median PFS of around 1 month (from 9 to 10 months) with an estimated HR of 1.17 (Supplementary Figure S2b). In both cases, unsurprisingly given the differences in trial design and treatment strategy, a large amount of heterogeneity was observed.

Prognostic effect of thrombocytosis

All trials, with the exception of OPTIMOX2 [25], provided baseline platelet data on >90% of all randomised patients; all trials provided platelet data equally across treatment arms. Across all trials combined there was no association between thrombocytosis incidence and treatment arm; however, there was a non-negligible association within OPTIMOX2 alone (33% in the intermittent arm vs 19% in the continuous arm). The incidence of thrombocytosis was comparable across trials, ranging from 17% to 32%. Across all patients with available data (n=5,659) the incidence was 28%, with a median platelet count of 322×10^9/l (IQR 255 to 414 $\times 10^9$/l). Hence, our *a priori* selected cut-point of 400×10^9/l represents the ~70th centile of the distribution.

Among patients *not* completing induction therapy, in the COIN and NORDIC VII trials we observed a significantly higher incidence of thrombocytosis than in the primary analysis sample (35% vs 29%, p=0.019 for COIN; 38% vs 26%, p=0.067 for NORDIC VII; Table 2). However, no other trials showed a significant difference.

Figure 4 shows a consistently poor prognostic effect associated with raised vs normal platelets, regardless of whether all therapy was stopped in the intermittent arm or oxaliplatin alone demonstrated in Figure S4 (overall pooled effect HR 1.42 [95% CI 1.25-1.61]). OPTIMOX2 (HR 1.19 [95% CI 0.68-2.10]) and GISCAD (HR 0.99 [95% CI 0.68-1.43]) were the only two trials with a hazard ratio more consistent with a null effect than with the pooled effect.

Supplementary Figure S3 suggests that despite the poorer prognosis for patients in the COIN trial, the effect of raised platelets is equally detrimental. Results for PFS were comparable to those for OS, with HRs estimated at 1.25 among trials with a "treatment break" comparator (including HR=1.41 for the COIN trial), and HR=1.18 among trials with a "maintenance" comparator (Supplementary Figure S5).

Interaction between treatment strategy and raised platelets

Because the COIN trial originally generated the thrombocytosis interaction hypothesis [11], for this analysis the COIN trial was treated as a development dataset, with the remaining trials treated as validation datasets. Table 2 shows that, within the primary analysis sample, the two trial subgroups ("complete stop" and "stop oxaliplatin only") each have a similar number of patients (n=1,471 and n=1,268 respectively) as the COIN "development" dataset (n=1,265). Since numbers of observed deaths are also similar (n=1,157, n=894 and n=927 respectively), we may assume that the power of each of the hypothesis-validating datasets is broadly comparable to that of the development dataset, at least in the absence of between-trial heterogeneity.

Figure 5 shows the treatment effect for each trial of intermittent versus continuous therapy by platelet subgroup, together with the interaction effect (i.e. the ratio of hazard ratios). It is clear that raised platelet count is not predictive of a detriment in OS within the validation set of trials with a removal of all therapy in the intermittent phase. Although the observed interaction HRs are somewhat inconsistent, there is no evidence of heterogeneity (I^2=0.0%), and only one trial (AIO 0207) has an interaction HR greater than 1 (i.e. an observed OS *benefit* from an intermittent strategy with raised platelets).

Results of the analysis of trials stopping oxaliplatin alone in the intermittent arm were less clear. The observed interaction HR is of substantial magnitude (HR=1.36) and two of the three trials (Nordic VII

being the exception) have interaction HRs consistent with this. Despite this observation of what might be termed "clinical heterogeneity", *statistical* heterogeneity remains negligible (I^2=0.0%); the width of the pooled confidence interval is due mostly to the correction for low numbers of studies [22]. However, that is rather the point: with only three studies, there is insufficient evidence to draw a firm conclusion regarding the predictive effect of raised platelets on OS with a removal of oxaliplatin only in the intermittent phase.

As a sensitivity analysis, we fitted a meta-analysis model for the interaction between treatment and the effect of platelet count as a continuous measurement. Tests for non-linearity (not shown) suggested that a simple linear association would be appropriate. The results (Supplementary Figure S6) for trials with a "treatment break" comparator strategy were consistent with the primary analyses (Figure 5). For trials with a "maintenance" comparator strategy, the Nordic VII trial was now consistent with the other two trials; although again, the correction for low number of studies under our chosen model [22] resulted in a non-statistically significant effect at the 5% level. Use of an alternative cut-point of 450×10^9/l, as suggested by some as a standardised upper limit of normal for platelets, showed a similar trend (data not shown).

PFS results were again broadly consistent with the OS results; with interaction HRs estimated at HR=0.98 among trials with a "treatment break" comparator but HR=1.36 for COIN; and HR=1.26 among trials with a "maintenance" comparator, with minimal statistical heterogeneity throughout (Supplementary Figure S7).

Discussion and Conclusions

The use of intermittent chemotherapy remains controversial in the care of patients with advanced colorectal cancer. In this analysis, we have accumulated a large IPD set exploring the role of

intermittent versus continuous chemotherapy in patients with advanced colorectal cancer. This large IPD meta-analysis demonstrates three important messages.

First, OS is not affected by the use of an intermittent systemic anti-cancer therapy strategy, whether that be a complete break from therapy or use of a maintenance therapy, when compared with a continuous therapy strategy. This finding is in agreement with previous studies [1] [2] [3] [8]. The evidence for an effect on OS from intermittent versus continuous therapy is heterogeneous, but the overall pooled results, are strongly suggestive of no difference. Although certain trials, notably CAIRO3 [4] and AIO 0207 [5], show a significant detriment in progression-free survival with intermittent therapy, this does not appear to translate into an OS detriment in this large dataset. Therefore, intermittent therapy, whether using a maintenance approach or complete break in systemic therapy, remains an acceptable alternative to a continuous treatment strategy. This needs to be considered in light of patient toxicity, desires for normal life and health care related costs.

Second, we have confirmed the well-recognised poor prognostic effect of raised platelet count at baseline. Thrombocytosis is confirmed as a poor prognostic factor in patients with advanced colorectal cancer; although the effect is noticeably larger in the COIN and AIO 0207 trials, and there is notable between-trial heterogeneity. The mechanism for this warrants further research as agents targeting the underlying mechanism may have significant benefit in colorectal and other cancers.

Third, we have failed to validate our hypothesis that thrombocytosis is a predictive biomarker of treatment strategy effectiveness. There is no consistent evidence regarding an interaction effect between intermittent versus continuous therapy and thrombocytosis among patients completing induction therapy. As a result, we amended the inclusion criteria for the FOCUS4 trial to allow inclusion of patients with thrombocytosis. Overall, trials where all treatment was removed in the intermittent phase (excluding COIN) combine to produce a null effect with no significant heterogeneity; although the AIO 0207 trial [5] is an outlier, being more aligned with COIN than with

the other trials. This is consistent with the results of a previous IPD meta-analysis of the AIO 0207 and CAIRO3 trials alone [6] which suggested a small but nevertheless non-significant predictive effect on OS. Interestingly, the AIO 0207/CAIRO3 study [6] did observe a significant predictive effect on PFS, after adjustment for potential confounders. Our study did not aim to assess PFS other than in an exploratory capacity, and did not have access to covariate data from all trials. With those limitations taken into account, however, the data we have available does not suggest either that covariate adjustment has a substantial impact on estimates (Supplementary Table S8), or that thrombocytosis is any more predictive of PFS than of OS (Supplementary Figure S7).

Finally, there was some evidence to suggest that a raised platelet count predicts for poor outcomes with removal of oxaliplatin in the intermittent phase, particularly when using a higher cut-off of 450×10^9/l. Although worthy of further investigation, this evidence comes from a minority of the total evidence base.

The mechanism underlying the ability of intermittent therapy to control cancer in the long run as effectively as continuous therapy, despite inferior progression-free survival, requires further study. Studies of ctDNA have revealed the emergence of specific genetic drivers of resistance to EGFR-targeted therapy in advanced colorectal cancer, which then diminish during a period off therapy [28]. This observation feeds into a wider understanding of tumour evolution driven by selective pressure due to therapeutic intervention, which is gaining increasing traction. This has been ably developed by Zhang et al [29] who suggest that appropriately-timed withdrawal of treatment can allow residual populations of sensitive cells to exploit their fitness advantage at the expense of the less-fit resistant phenotypes.

This study successfully sought individual participant data (IPD) from the largest eligible trials; overall we obtained data from 73% of relevant patients. Availability of IPD allowed us to harmonize across trials the subset of patients who successfully commenced the maintenance phase of therapy,

minimizing the risk of bias from comparing between trial designs with different timings of randomization with respect to phases of treatment strategy. In contrast to the published-data network analysis of Sonbol et al [8], we pooled data from all trial protocols where the treatment regimen in the intermittent phase was compared to a similar regimen with one or more elements removed, with the only proviso being that the "continuous" treatment regimen did not include any element that was not present in the induction phase. Hence, our analysis represents the largest and most closely-harmonized comparison of intermittent strategies currently in use in the field of advanced colorectal cancer.

The main limitation of our study was the lack of data on prognostic factors other than platelet count. This was due to original data requests being made in response to the COIN finding [11] of a predictive effect from thrombocytosis specifically. However, we note that all included studies were randomised controlled trials, such that major imbalances in prognostic factor covariates is unlikely. Furthermore, a sensitivity analysis including additional appropriate published data (Supplementary Figure S8), and a sensitivity analysis making use of the limited covariate data available to us (Supplementary Tables S1 and S2), showed no significant differences in results. Whilst it is hypothesised that poorer prognosis patients might requires some form of ongoing therapy to prevent a loss of tumour control beyond recovery, review of the larger phase III studies indicate that simple markers of poor prognosis do not define a population that require a maintenance or continuation strategy. COIN explored sixteen poor prognostic factors and identified only thrombocytosis as significant, whilst CAIRO3 and AIO 0207 pooled data and explored twelve factors in 871 patients identifying no significant subgroups. Further work to explore a larger pooled analysis is planned.

We conclude that thrombocytosis alone should not be used as a predictive biomarker for a continuous versus intermittent therapy strategy. An intermittent treatment strategy is not associated with impaired OS and should be a routinely considered option for patients with disease control over the first 3-6 months of standard of care first line therapy for aCRC. Additionally, given the situation of the

ongoing COVID19 pandemic enhanced efforts to reduce patient exposure and remove patient risk should be fully explored. Future analyses should seek to identify the mechanism linking thrombocytosis with poor outcome and to assess whether therapeutic strategies including the use of anti-cytokine therapies, might have a role to play to improve survival in these patients.

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Tables

Table 1 - Summary of eligible studies comparing intermittent with continuous treatment strategies

N = number of patients; Alloc. ratio = allocation ratio; Fp = fluoropyrimidine; 5FU = infusional 5-fluorouracil; Cap. = capecitabine; Ox = oxaliplatin; Ir = irinotecan; Cet. = cetuximab; Bev. = bevacizumab; maint. = maintenance therapy during intermittent phase

Ordered by years recruited; most recent first

Trial name (years recruited)	Trial type	Total N randomised (alloc. ratio)	Length of initial period; relative timing of randomisation	Restart procedure	Fp used during induction phase	Regimens during induction phase	Regimens during intermittent phase
PRODIGE-9 [30] (2010-13)	Randomised Phase III	491 (1:1)	24 weeks; before	On progression; repeat until failure	5FU	IrFp + Bev. IrFp + Bev.	Bevacizumab No treatment
Luo et al. [31] (2010-13)	Randomised Phase III	274 (1:1)	18-24 weeks; after	No restart; fail at first progression	Any	OxFp OxFp	Capecitabine No treatment
AIO 0207 [5] (2009-13)	Randomised Phase III	472 (1:1:1)	24 weeks; after	On progression; repeat until failure	Any	OxFp + Bev. OxFp + Bev. OxFp + Bev.	Fp + Bev. Bevacizumab No treatment

Yalcin et al. [30] (2008-09)	Randomised Phase III	123 (1:1)	18 weeks; before	No restart; fail at first progression	Cap.	OxFp + Bev. OxFp + Bev.	Same Fp + Bev. maint.
SAKK 41/06 [24] (2007-12)	Randomised Phase III	265 (1:1)	16-24 weeks; after	No restart; fail at first progression	Any	OxFp/IrFp + Bev. OxFp/IrFp + Bev.	Bevacizumab No treatment
CAIRO 3 [4] (2007-12)	Randomised Phase III	558 (1:1)	18 weeks; after	On progression; single restart only	Cap.	OxFp + Bev. OxFp + Bev.	Fp + Bev. No treatment
COIN-B [9] (2007-10)	Randomised Phase II	226 (1:1)	12 weeks; before	On progression; repeat until failure	5FU	OxFp + Cet. OxFp + Cet.	Cetuximab No treatment
TTD MACRO [13] (2006-08)	Randomised Phase III	480 (1:1)	18 weeks; before	No restart; fail at first progression	Cap.	OxFp + Bev. OxFp + Bev.	Same Bev. maint.
COIN [11] (2005-08)	Randomised Phase III	2,445 (1:1:1)	12 weeks; before	On progression; repeat until failure	5FU/Cap. (free choice)	OxFp OxFp + Cet. OxFp	Same Same No treatment
NORDIC VII [10] (2005-07)	Randomised Phase III	571 (1:1:1)	16 weeks; before	On progression; repeat until failure	5FU	OxFp OxFp + Cet. OxFp + Cet.	Same Same Cet. maint.

OPTIMOX2 [25] (2004-06)	Randomised Phase II	216 (1:1)	12 weeks; before	On progression; repeat until failure	5FU	OxFp OxFp	Fluoropyrimidine No treatment
GISCAD [12] (2001-05)	Randomised Phase III	293 (1:1)	8 weeks; before	After fixed time; repeat until progression	5FU	IrFp IrFp	Same No treatment
OPTIMOX1 [26] (2000-02)	Randomised Phase II	623 (1:1)	12 weeks; before	After fixed time; repeat until progression	5FU	OxFp OxFp	Same Fp maint.
CR06 B [27] (1996-00)	Randomised Phase III	354 (1:1)	12 weeks; after	On progression; single restart only	FU alone/ FU+ Calcium Folinate/ raltitrexed	Fp alone Fp alone	Same No treatment
Mikami et al [31] (reported 2011)	Randomised Phase II	60 (1:1)	12 weeks; before	After fixed time; repeat until progression	5FU	OxFp OxFp	Same Fp maint.
CONcePT [32] (reported 2008)	Randomised Phase III	139 (1:1) *	16 weeks; before	After fixed time; repeat until progression	5FU	OxFp + Bev. OxFp + Bev.	Same Fp + Bev. maint.
		39	12 weeks; after		5FU	IrFp	Same

Alexopoulos and Kotsori [33] (reported 2006)	Randomised Phase II	(1:1)		No restart; fail at first progression		IrFp	No treatment

* Full trial design was 2x2 factorial; however the intermittent vs continuous comparison may be considered as a 1:1 randomisation

Table 2 – Numbers of patients in primary analysis sample, and incidence of thrombocytosis

Trial name	Length of initial period	N available [N missing†]	Primary analysis sample: N (%) completing induction	N (%) of primary analysis sample with baseline platelets available	N (%) with thrombo-cytosis
Planned complete stop of all therapy					
AIO 0207	24 weeks	470 [2]	454 (97%)	450 (99%)	141 (31%)
CAIRO 3	18 weeks	557 [1]	557 (100%)	506 (91%)	162 (32%)
COIN-B	12 weeks	226 [0]	176 (78%)	176 (100%)	41 (23%)
COIN*	12 weeks	1,630 [0]	1,270 (78%)	1,265 (>99%)	363 29%)
OPTIMOX2	12 weeks	202 [14]	186 (92%)	88 (47%)	25 (28%)
GISCAD	8 weeks	293 [44]	264 (90%)	251 (95%)	42 (17%)
Planned stop of oxaliplatin					
TTD MACRO	18 weeks	480 [0]	385 (80%)	384 (>99%)	89 (23%)
NORDIC VII*	16 weeks	381 [2]	329 (86%)	328 (>99%)	86 (26%)
OPTIMOX1	12 weeks	620 [3]	559 (90%)	556 (>99%)	137 (25%)

* The continuous-strategy cetuximab arm from COIN and the continuous OxFp arm from NORDIC VII were not included in the primary analysis sample as there was no directly comparable intermittent strategy within the trial design

† Reasons for missing data, by trial:

AIO 0207: Two patients were excluded due to absence of follow-up data

CAIRO3: One patient withdrew informed consent post-randomisation

OPTIMOX2: Data on 14 patients, deemed ineligible post-randomisation, were not available for this analysis

GISCAD: A per-protocol approach was taken by the investigators [14]; only data on the per-protocol sample was available for this analysis

NORDIC VII: A total of 5 patients were excluded from the ITT analysis post-randomisation, but their allocation was not reported. Since one of the three arms is not included in the primary analysis sample for the current project, the precise number missing is unknown

OPTIMOX1: Data on three patients, deemed ineligible post-randomisation, were not available for this analysis.

Figure legends

Figure 1 – PRISMA flow diagram

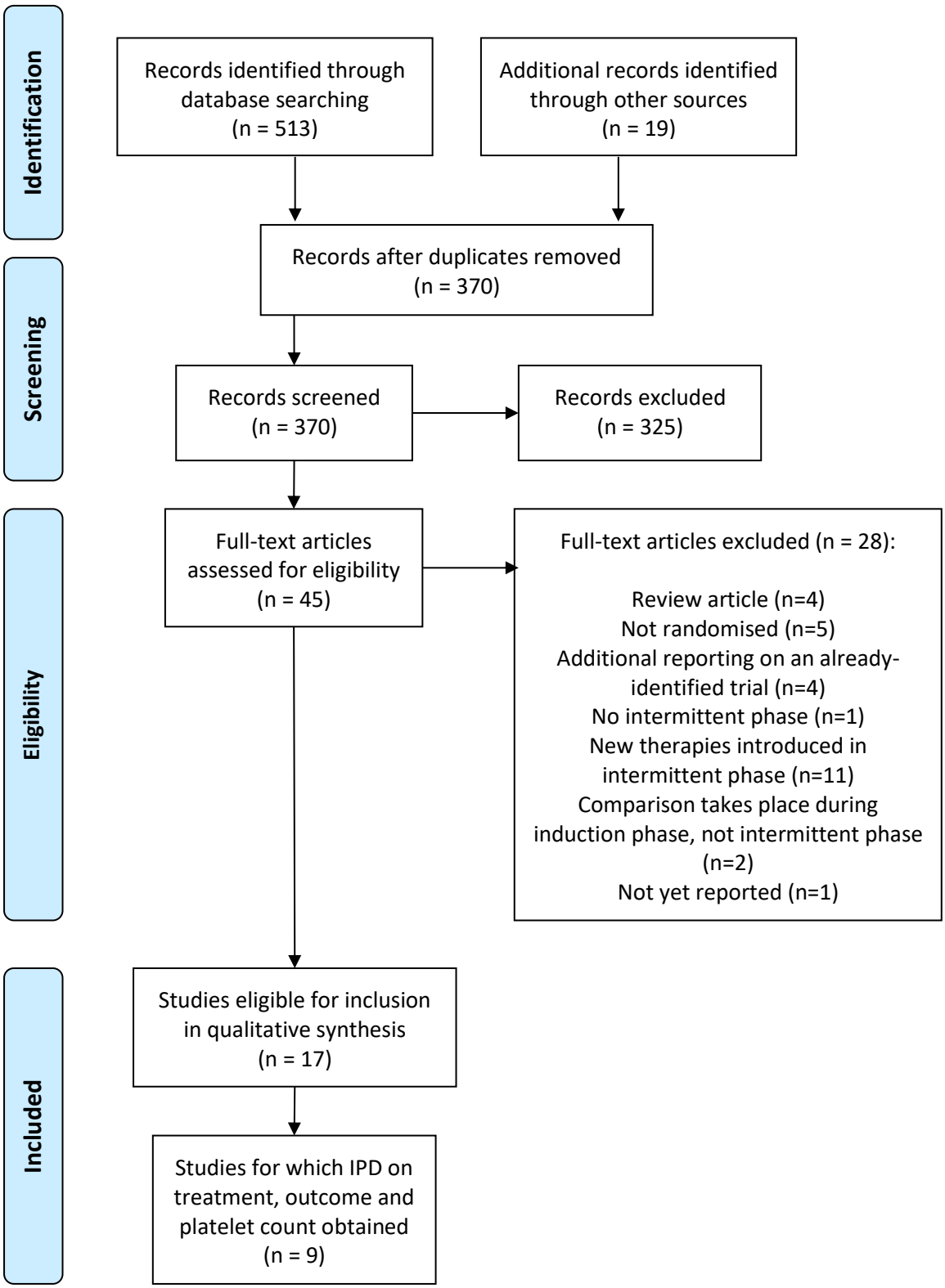


Figure 2 – Effect of intermittent versus continuous therapy on OS

Figure 2a: Kaplan-Meier curves for OS in all patients from all trials presented by intermittent versus continuous treatment strategy

Figure 2b: Forest plot of OS by trial comparing intermittent versus continuous treatment strategies. Strategies are arranged into two subgroups, defined by whether all therapy was stopped in the intermittent treatment arm, or whether only oxaliplatin was stopped.

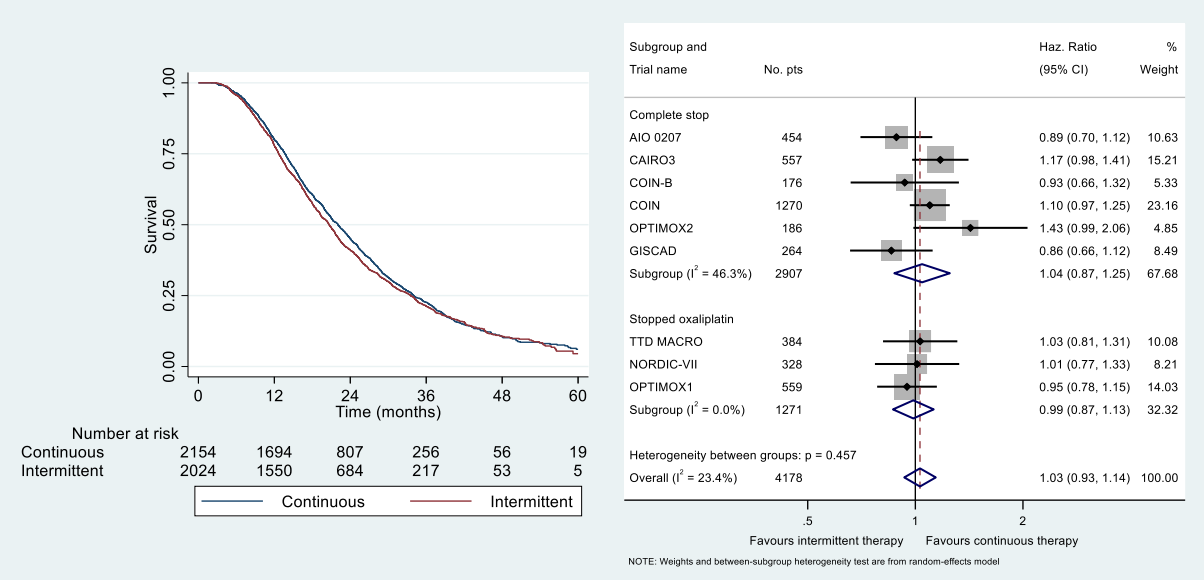


Figure 3 – Kaplan Meier curves comparing overall survival by treatment strategy.

Figure 3a: Kaplan Meier curve comparing overall survival for continuous strategy compared to a complete stop in treatment intermittent strategy.

Figure 3b: Kaplan Meier curve comparing overall survival for continuous strategy compared to a maintenance intermittent strategy.

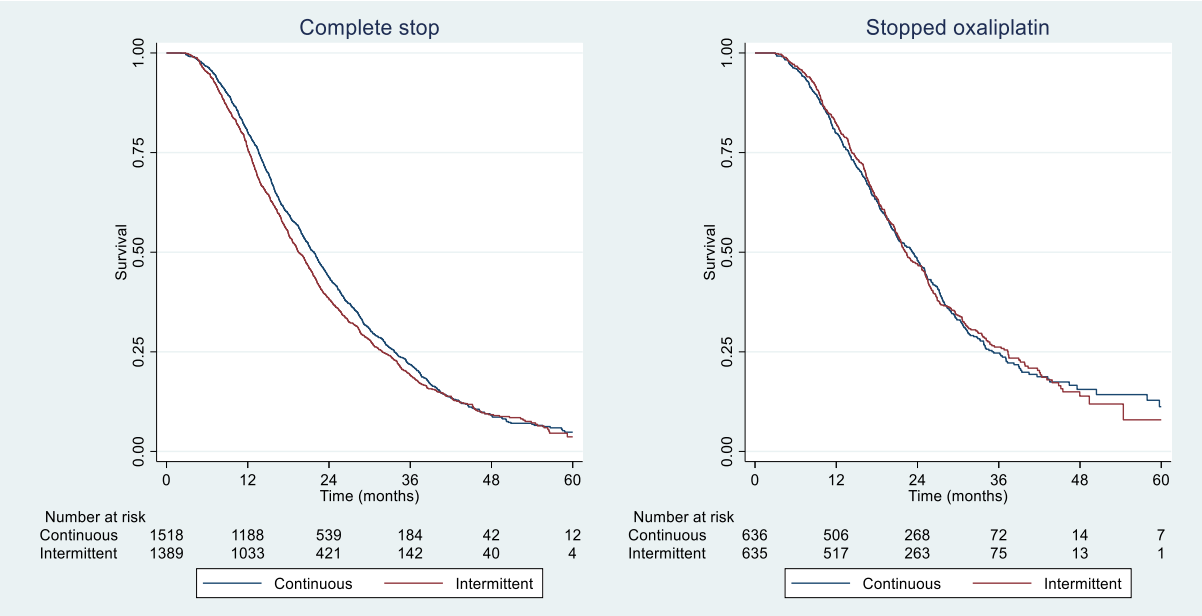


Figure 4 - OS prognostic effect of baseline thrombocytosis

Figure 4a: Kaplan-Meier curves for OS in all patients from all trials presented by raised versus normal platelets

Figure 4b: Forest plot of OS by trial comparing patients with raised versus normal platelets. Strategies are arranged into two subgroups, defined by whether all therapy was stopped in the intermittent arm, or whether oxaliplatin only was stopped.

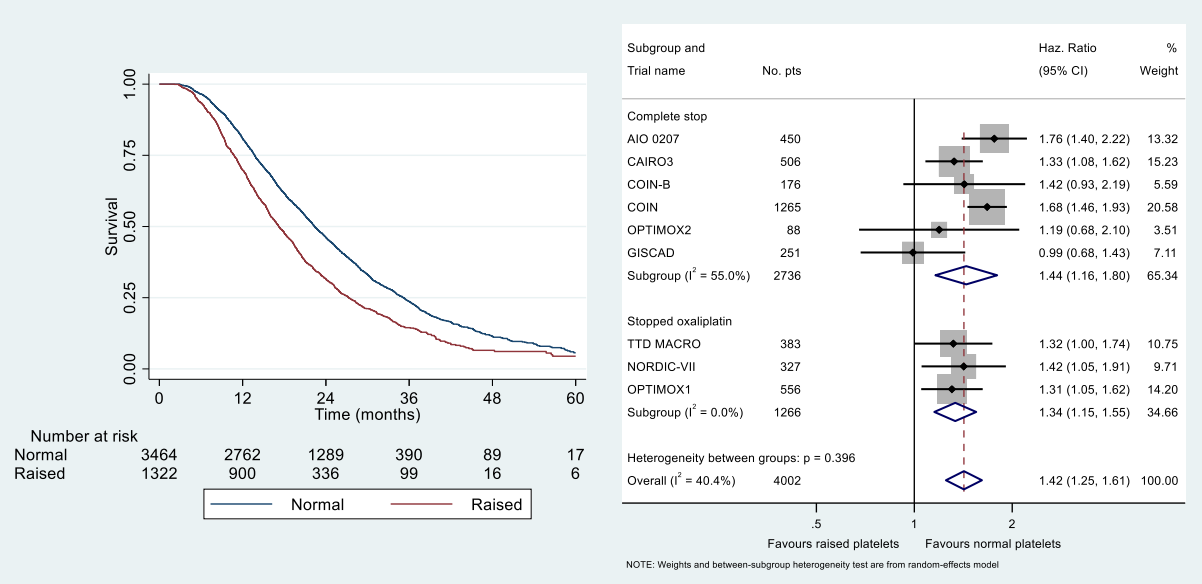
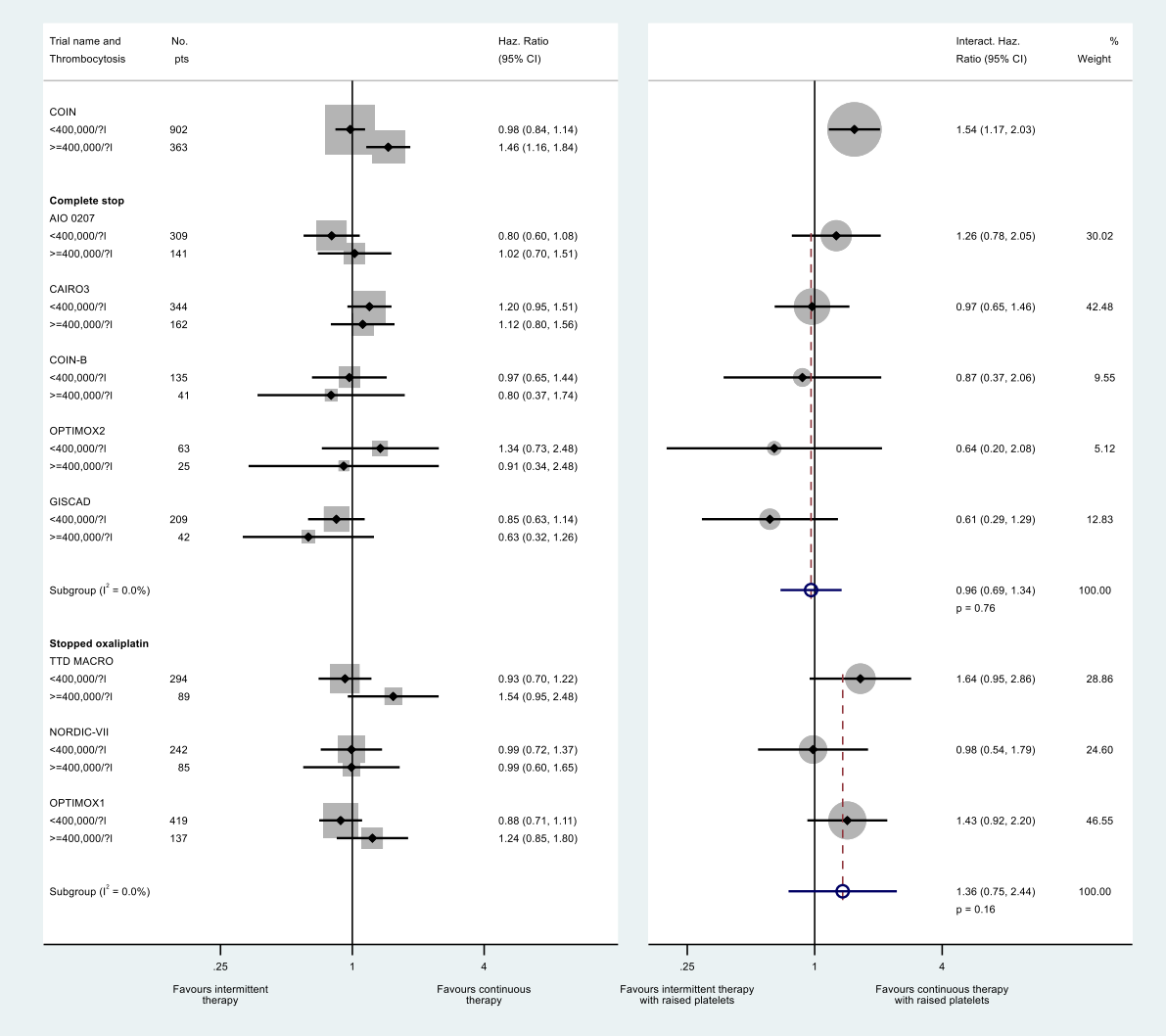
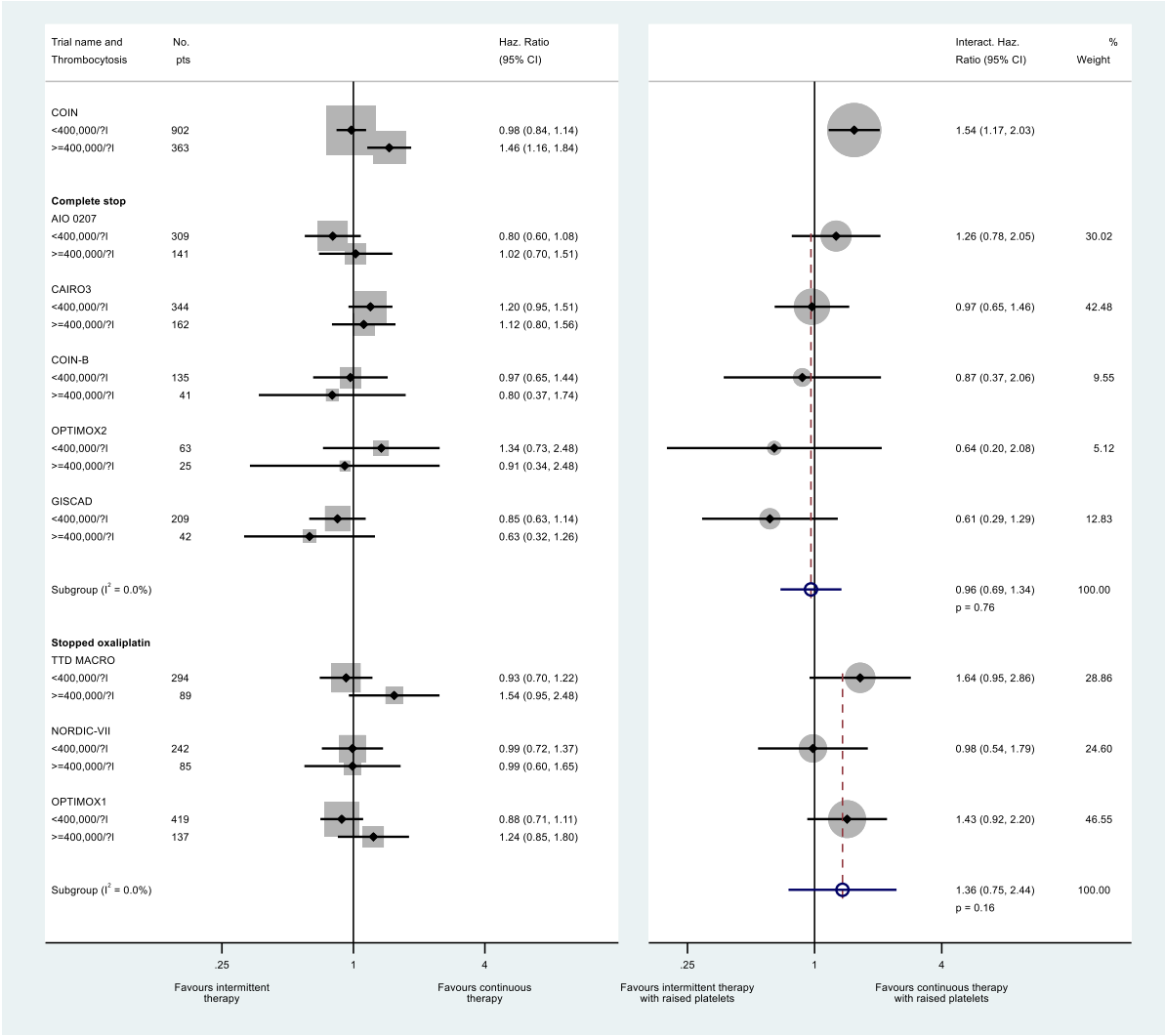


Figure 5 – OS interaction effect between treatment strategy and thrombocytosis

Figure 5a: Forest plot of OS by trial comparing intermittent versus continuous therapy for subgroups with raised or normal platelets. Strategies are arranged into two subgroups, defined by whether all therapy was stopped in the intermittent arm, or whether oxaliplatin only was stopped.

Figure 5b: Forest plot of tests of interaction for OS by trial between treatment strategy and thrombocytosis.




Trial name and Thrombocytosis
No. pts
Haz. Ratio (95% CI)
Interact. Haz. Ratio (95% CI)
% Weight
COIN
<400,000/?l 902 0.98 (0.84, 1.14)
>=400,000/?l 363 1.46 (1.16, 1.84)
1.54 (1.17, 2.03)
Complete stop
AIO 0207
<400,000/?l 309 0.80 (0.60, 1.08) 1.26 (0.78, 2.05) 30.02
>=400,000/?l 141 1.02 (0.70, 1.51)
CAIRO3
<400,000/?l 344 1.20 (0.95, 1.51) 0.97 (0.65, 1.46) 42.48
>=400,000/?l 162 1.12 (0.80, 1.56)
COIN-B
<400,000/?l 135 0.97 (0.65, 1.44) 0.87 (0.37, 2.06) 9.55
>=400,000/?l 41 0.80 (0.37, 1.74)
OPTIMOX2
<400,000/?l 63 1.34 (0.73, 2.48) 0.64 (0.20, 2.08) 5.12
>=400,000/?l 25 0.91 (0.34, 2.48)
GISCAD
<400,000/?l 209 0.85 (0.63, 1.14) 0.61 (0.29, 1.29) 12.83
>=400,000/?l 42 0.63 (0.32, 1.26)
Subgroup (I² = 0.0%) 0.96 (0.69, 1.34) 100.00
p = 0.76
Stopped oxaliplatin
TTD MACRO
<400,000/?l 294 0.93 (0.70, 1.22) 1.64 (0.95, 2.86) 28.86
>=400,000/?l 89 1.54 (0.95, 2.48)
NORDIC-VII
<400,000/?l 242 0.99 (0.72, 1.37) 0.98 (0.54, 1.79) 24.60
>=400,000/?l 85 0.99 (0.60, 1.65)
OPTIMOX1
<400,000/?l 419 0.88 (0.71, 1.11) 1.43 (0.92, 2.20) 46.55
>=400,000/?l 137 1.24 (0.85, 1.80)
Subgroup (I² = 0.0%) 1.36 (0.75, 2.44) 100.00
p = 0.16
.25
1
4
Favours intermittent therapy
Favours continuous therapy
Favours intermittent therapy with raised platelets
Favours continuous therapy with raised platelets

Supplementary Figure S1 – Kaplan-Meier plots presenting OS for intermittent versus continuous therapy for COIN versus other trials

Supplementary Figure S2 - Effect of intermittent versus continuous therapy on PFS

Figure S2a: Kaplan-Meier curves for PFS in all patients from trials where all therapy was stopped in the intermittent arm

Figure S2b: Kaplan-Meier curves for PFS in all patients from trials where oxaliplatin only was stopped in the intermittent arm

Figure S2c: Forest plot of PFS by trial comparing intermittent versus continuous treatment strategies. Strategies are arranged into two subgroups, defined by whether all therapy was stopped in the intermittent arm, or whether oxaliplatin only was stopped.

Supplementary Figure S3 – Kaplan-Meier plots presenting OS for raised versus normal platelets for COIN versus other trials

Supplementary Figure S4 - Kaplan-Meier curves showing the effect of thrombocytosis on OS

Figure S4a: Trials where the intermittent schedule was “complete break”

Figure S4b: Trials where the intermittent schedule was “maintenance strategy omitting oxaliplatin”

Supplementary Figure S5 – PFS prognostic effect of baseline thrombocytosis

Figure S5a: Kaplan-Meier curves for PFS in all patients from trials where all therapy was stopped in the intermittent arm

Figure S5b: Kaplan-Meier curves for PFS in all patients from trials where oxaliplatin only was stopped in the intermittent arm

Figure S5c: Forest plot of PFS by trial, presented by raised vs normal platelets. Strategies are arranged into two subgroups, defined by whether all therapy was stopped in the intermittent arm, or whether oxaliplatin only was stopped.

Supplementary Figure S6 – Interaction effect between treatment strategy and platelet count as a continuous measurement

Note: Interaction HRs are interpretable as the change in the effect of intermittent versus continuous therapy for each increase of $100x10^9$/l in platelet count.

Supplementary Figure S7 – PFS interaction effect between treatment strategy and thrombocytosis

Other supplementary material

Supplementary information: Search strategy

Databases:
Embase <1974 to 2018 August 03>
Ovid MEDLINE(R) <1946 to July Week 4 2018>

1 random$.tw. (2098203)
2 colorectal.tw. (287165)
3 metastatic.tw. (453057)
4 advanced.tw. (807494)
5 2 and (3 or 4) (62234)
6 first line.tw. (160170)
7 initial therapy.tw. (17041)
8 initial treatment.tw. (47918)
9 (no$ adj2 expos$ adj2 therapy).tw. (84)
10 (no$ adj2 expos$ adj2 chemotherapy).tw. (147)
11 (no$ adj2 expos$ adj2 treatment).tw. (428)
12 6 or 7 or 8 or 9 or 10 or 11 (220881)
13 maintenance.tw. (527731)
14 continu$.tw. (1939783)
15 discontinu$.tw. (266565)
16 stop-and-go.tw. (770)
17 treatment holiday$.tw. (132)
18 intermittent$.tw. (172664)
19 interrupt$.tw. (138191)
20 free interval.tw. (16837)
21 free period.tw. (7386)
22 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (2885348)
23 1 and 5 and 12 and 22 (524)
24 limit 23 to yr="1990 - 2017" (513)
25 remove duplicates from 24 (370)

Supplementary Table S1 – Available covariate data, and adjusted interaction effects

HR = hazard ratio

Covariate	**Trial** COIN	AIO 0207	COIN-B	CAIRO3	OPTIMOX 2	GISCAD	TTD MACRO	NORDIC VII	OPTIMOX 1
Age	✓		✓	✓	✓		✓	✓	✓
Sex	✓		✓	✓	✓		✓	✓	✓
Prior adj.	✓		✓	✓	✓		✓	✓	✓
Response	✓		✓		✓				✓
WHO PS	✓		✓	✓	✓		✓	✓	✓
Resection	✓		✓	✓			✓		
Synch	✓		✓		✓				✓
Location	✓		✓		✓				✓
No. mets	✓		✓		✓		✓	✓	✓
Time from primary diagn.	✓		✓		✓				✓
OS									
Unadjusted Interaction HR (95% CI)	1.53 (1.16, 2.02)	1.26 (0.78, 2.05)	0.87 (0.37, 2.06)	0.97 (0.65, 1.46)	0.64 (0.20, 2.08)	0.61 (0.29, 1.29)	1.65 (0.95, 2.86)	1.01 (0.56, 1.83)	1.43 (0.92, 2.20)
Adjusted Interaction HR (95% CI)	1.69 (1.27, 2.24)	N/A	0.87 (0.35, 2.17)	1.10 (0.73, 1.66)	0.65 (0.17, 2.45)	N/A	1.58 (0.91, 2.76)	0.54 (0.24, 1.18)	1.38 (0.89, 2.15)
PFS									
Unadjusted Interaction HR (95% CI)	1.36 (1.03, 1.79)	1.02 (0.67, 1.57)	0.67 (0.28, 1.58)	1.13 (0.77, 1.66)	0.67 (0.25, 1.82)	0.81 (0.41, 1.61)	1.36 (0.82, 2.26)	1.19 (0.71, 2.00)	1.26 (0.85, 1.87)
Adjusted Interaction HR (95% CI)	1.43 (1.08, 1.90)	N/A	0.58 (0.23, 1.46)	1.25 (0.85, 1.85)	0.64 (0.22, 1.85)	N/A	1.32 (0.79, 2.20)	1.11 (0.57, 2.16)	1.26 (0.84, 1.88)

Supplementary Table S2 – Estimated pooled adjusted effects using multivariate meta-analysis

For trials with covariate data available, bootstrapping was used to estimate the correlation between unadjusted and adjusted results. Then, multivariate meta-analysis was used to pool unadjusted and adjusted results simultaneously, accounting for their correlation where available. This approach is described in Riley RD et al. Multivariate meta-analysis using individual participant data. *Research Synthesis Methods* 2015; 6: 157. doi: 10.1002/jrsm.1129

Effect of intermittent versus continuous chemotherapy

Trial	Unadjusted (see Figure 2)	Heterogeneity	Adjusted * (see Suppl. Table S1)	Heterogeneity
Complete stop				
AIO 0207	0.89 (0.70, 1.12)		N/A	
CAIRO3	1.17 (0.98, 1.41)		1.19 (0.98, 1.41)	
COIN-B	0.93 (0.66, 1.32)		0.90 (0.64, 1.36)	
COIN	1.10 (0.97, 1.25)		1.11 (0.96, 1.25)	
OPTIMOX2	1.43 (0.99, 2.06)		1.30 (0.97, 2.10)	
GISCAD	0.86 (0.66, 1.12)		N/A	
Subgroup	1.02 (0.86, 1.22)	$\tau^2 = 0.021$	1.06 (0.79, 1.33)	$\tau^2 = 0.020$
Oxaliplatin stop				
TTD MACRO	1.03 (0.81, 1.31)		1.10 (0.81, 1.31)	
NORDIC-VII	1.01 (0.77, 1.33)		0.96 (0.71, 1.44)	
OPTIMOX1	0.95 (0.78, 1.15)		0.95 (0.78, 1.15)	
Subgroup	0.99 (0.87, 1.13)	$\tau^2 = 0.000$	1.00 (0.86, 1.13)	$\tau^2 = 0.000$
Overall	1.03 (0.95, 1.12)	$\tau^2 = 0.003$	1.06 (0.93, 1.15)	$\tau^2 = 0.006$

Prognostic effect of thrombocytosis

Trial	Unadjusted (see Figure 4)	Heterogeneity	Adjusted * (see Suppl. Table S1)	Heterogeneity
Complete stop				
AIO 0207	1.76 (1.40, 2.22)		N/A	
CAIRO3	1.33 (1.08, 1.62)		1.24 (1.01, 1.53)	
COIN-B	1.42 (0.93, 2.19)		1.26 (0.77, 2.04)	
COIN	1.66 (1.48, 1.86)		1.53 (1.35, 1.73)	
OPTIMOX2	1.19 (0.68, 2.10)		1.00 (0.54, 1.86)	
GISCAD	0.99 (0.68, 1.43)		N/A	
Subgroup	1.36 (1.11, 1.67)	$\tau^2 = 0.026$	1.22 (1.02, 1.47)	$\tau^2 = 0.000$
Oxaliplatin stop				

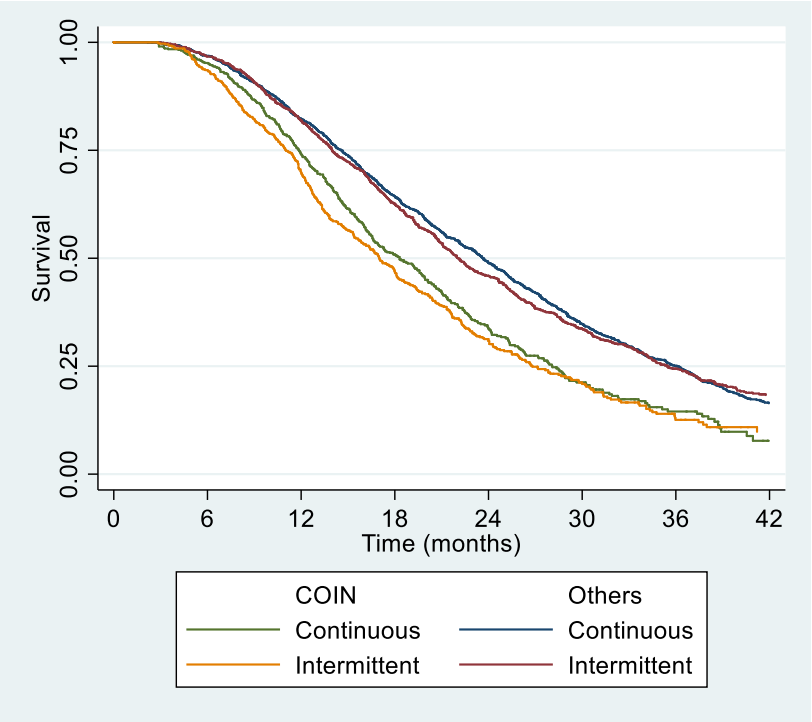
TTD MACRO	1.32 (1.00, 1.74)		1.17 (0.88, 1.55)	
NORDIC-VII	1.54 (1.21, 1.96)		1.44 (1.03, 2.02)	
OPTIMOX1	1.31 (1.05, 1.62)		1.15 (0.91, 1.45)	
Subgroup	1.38 (1.20, 1.59)	$\tau^2 = 0.000$	1.23 (1.05, 1.44)	$\tau^2 = 0.002$
Overall	1.44 (1.29, 1.61)	$\tau^2 = 0.011$	1.29 (1.13, 1.47)	$\tau^2 = 0.013$

Interaction between treatment strategy and raised platelets

Trial	Unadjusted (see Figure 5)	Heterogeneity	Adjusted * (see Suppl. Table S1)	Heterogeneity
COIN	1.54 (1.17, 2.03)		1.70 (1.28, 2.26)	
Complete stop				
AIO 0207	1.26 (0.78, 2.05)		N/A	
CAIRO3	0.97 (0.65, 1.46)		1.10 (0.73, 1.66)	
COIN-B	0.87 (0.37, 2.06)		0.87 (0.35, 2.17)	
OPTIMOX2	0.64 (0.20, 2.08)		0.65 (0.17, 2.45)	
GISCAD	0.61 (0.29, 1.29)		N/A	
Subgroup	0.96 (0.74, 1.25)	$\tau^2 = 0.000$	1.02 (0.71, 1.46)	$\tau^2 = 0.000$
Oxaliplatin stop				
TTD MACRO	1.64 (0.95, 2.86)		1.59 (0.91, 2.77)	
NORDIC-VII	0.98 (0.54, 1.79)		1.06 (0.58, 1.94)	
OPTIMOX1	1.43 (0.92, 2.20)		1.38 (0.89, 2.15)	
Subgroup	1.36 (1.01, 1.82)	$\tau^2 = 0.000$	1.35 (0.99, 1.84)	$\tau^2 = 0.003$
Overall	1.19 (0.98, 1.46)	$\tau^2 = 0.025$	1.26 (0.97, 1.64)	$\tau^2 = 0.038$

* Subgroup and Overall adjusted hazard ratios are obtained from a multivariate meta-analysis model which makes use of unadjusted data for trials where adjusted data was not available. Between-study heterogeneity was estimated using a REML random-effects model.

Supplementary Figure S1 – Kaplan-Meier plots presenting OS for intermittent versus continuous therapy for COIN versus other trials

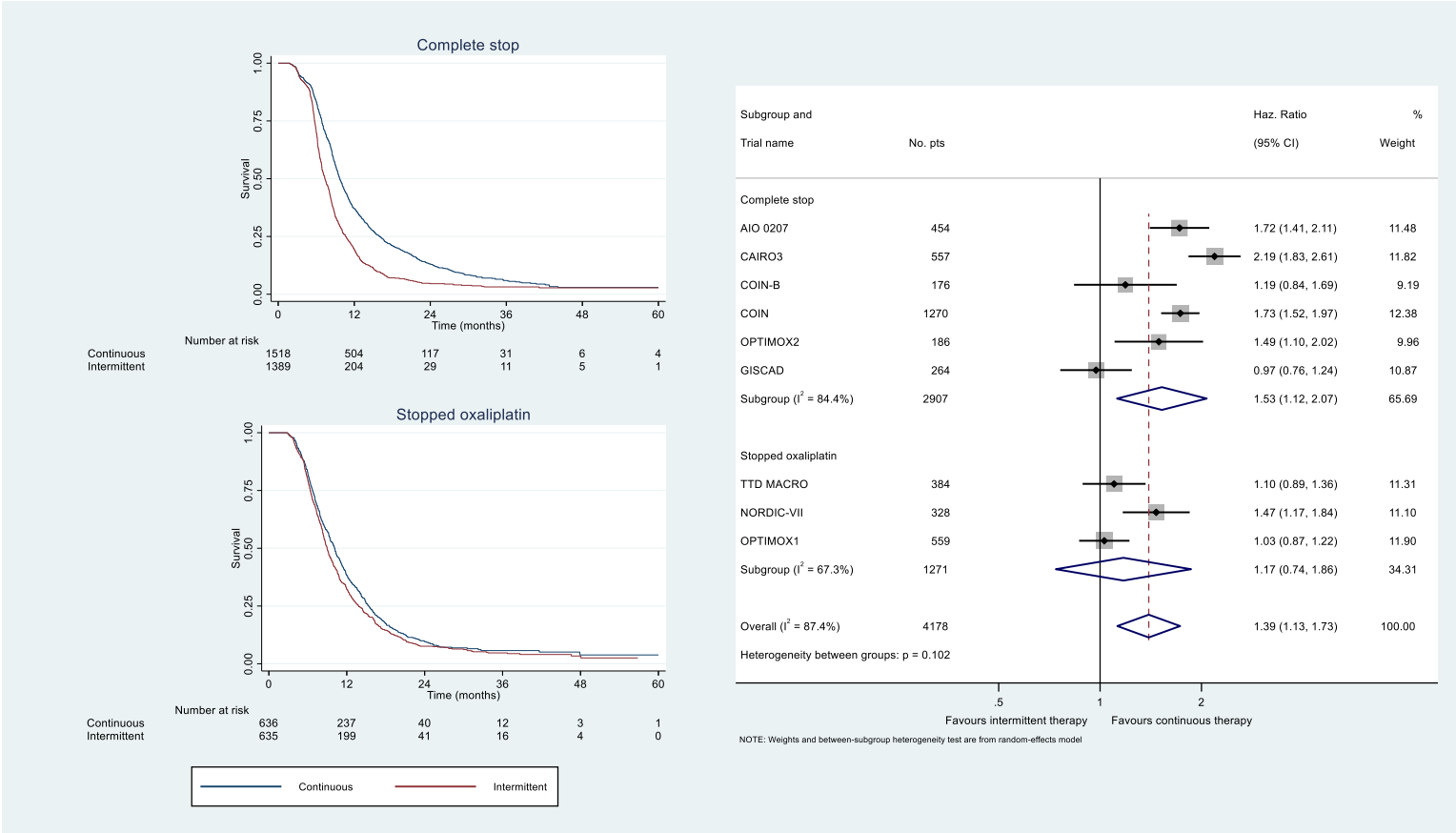

Survival
0.00
0.25
0.50
0.75
1.00
0
6
12
18
24
30
36
42
Time (months)
COIN
Continuous
Intermittent
Others
Continuous
Intermittent

Supplementary Figure S2 – Effect of intermittent versus continuous therapy on PFS

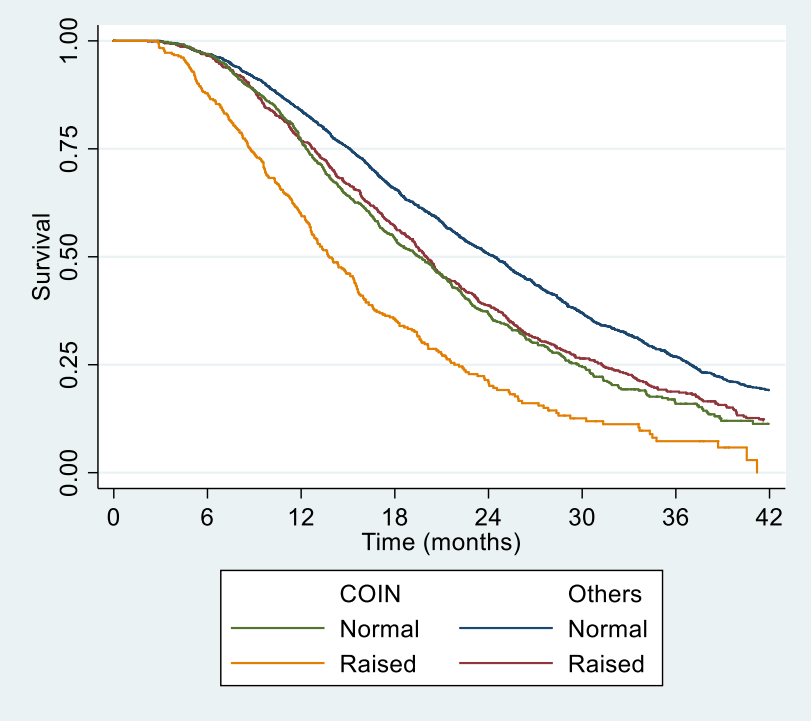
Figure S2a: Kaplan-Meier curves for PFS in all patients from trials where all therapy was stopped in the intermittent arm

Figure S2b: Kaplan-Meier curves for PFS in all patients from trials where oxaliplatin only was stopped in the intermittent arm

Figure S2c: Forest plot of PFS by trial comparing intermittent versus continuous treatment strategies. Strategies are arranged into two subgroups, defined by whether all therapy was stopped in the intermittent arm, or whether oxaliplatin only was stopped.



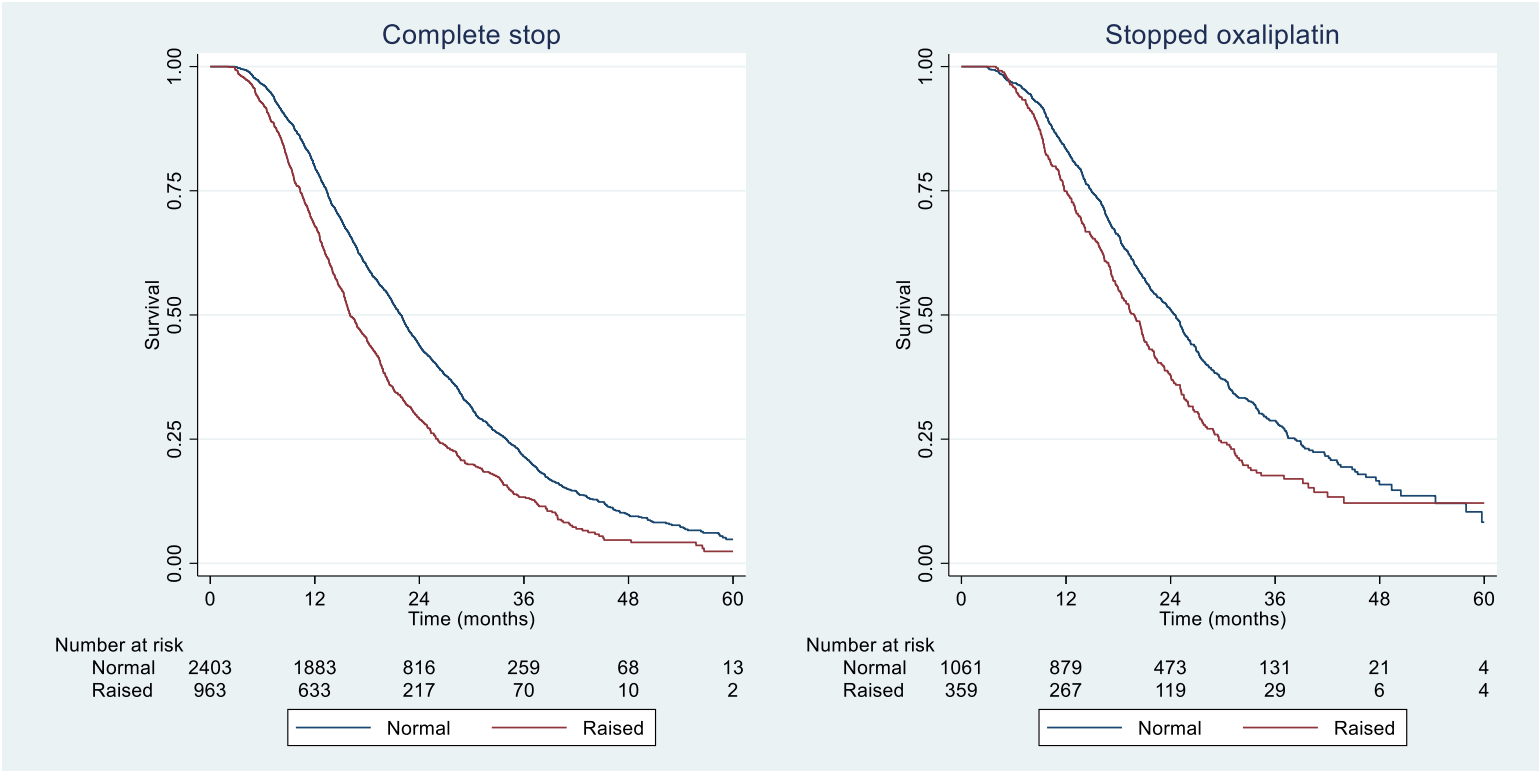
Supplementary Figure S3 – Kaplan-Meier plots presenting OS for raised versus normal platelets for COIN versus other trials



Supplementary Figure S4 – Kaplan-Meier curves showing the effect of thrombocytosis on OS

Figure S4a: Trials where the intermittent schedule was “complete break”

Figure S4b: Trials where the intermittent schedule was “maintenance strategy omitting oxaliplatin”

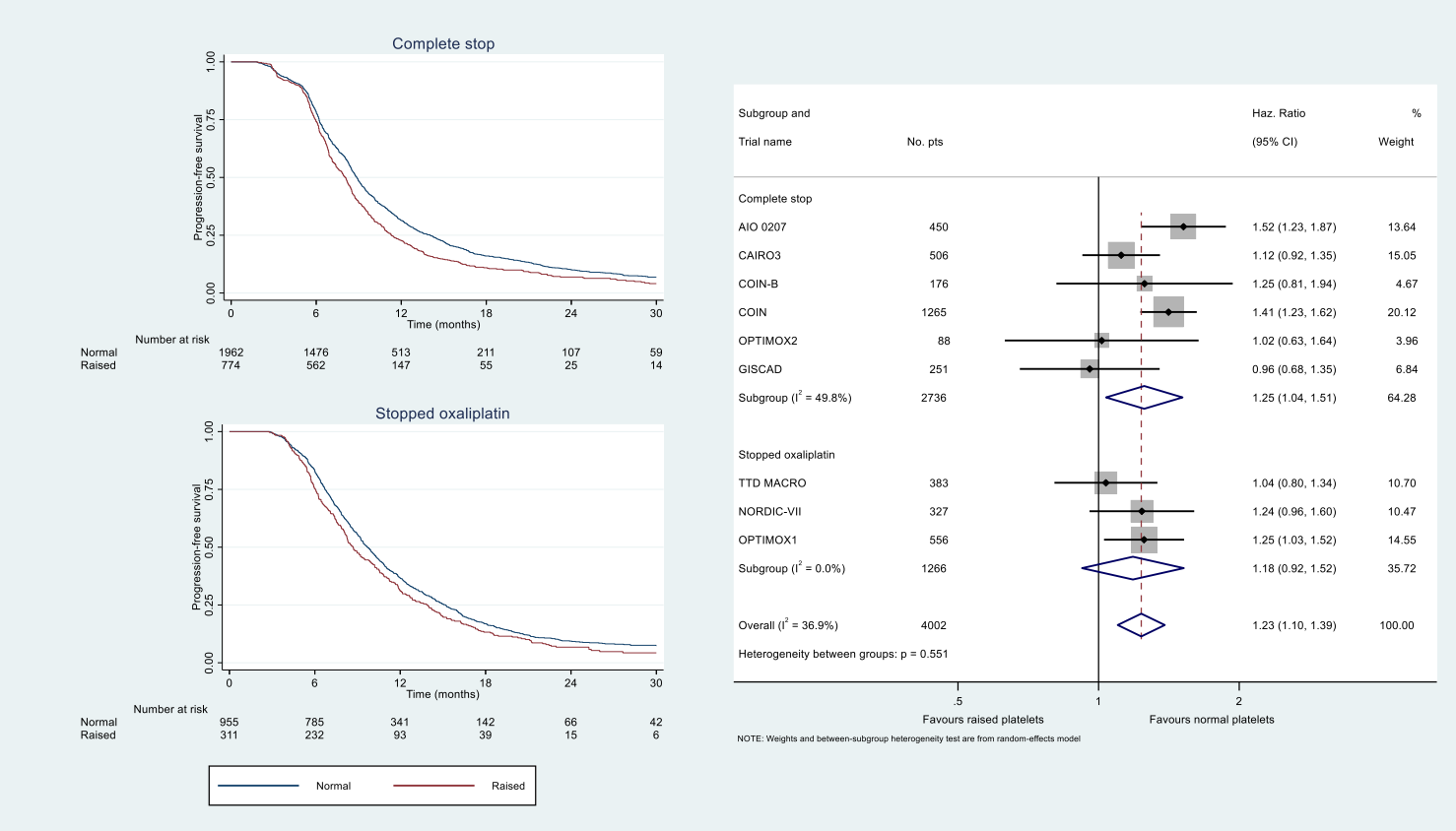


Supplementary figure S5 – PFS prognostic effect of baseline thrombocytosis

Figure S5a: Kaplan-Meier curves for PFS in all patients from trials where all therapy was stopped in the intermittent arm

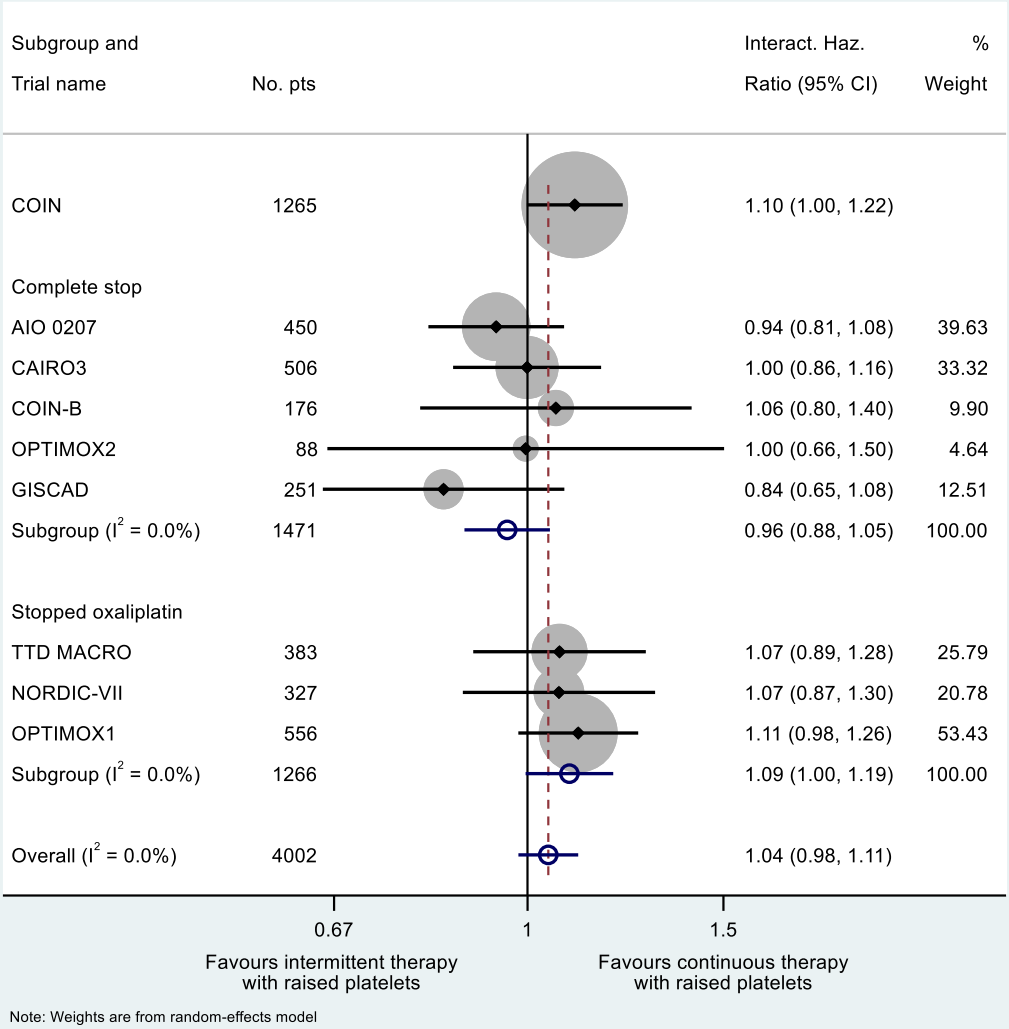
Figure S5b: Kaplan-Meier curves for PFS in all patients from trials where oxaliplatin only was stopped in the intermittent arm

Figure S5c: Forest plot of PFS by trial, presented by raised vs normal platelets. Strategies are arranged into two subgroups, defined by whether all therapy was stopped in the intermittent arm, or whether oxaliplatin only was stopped.

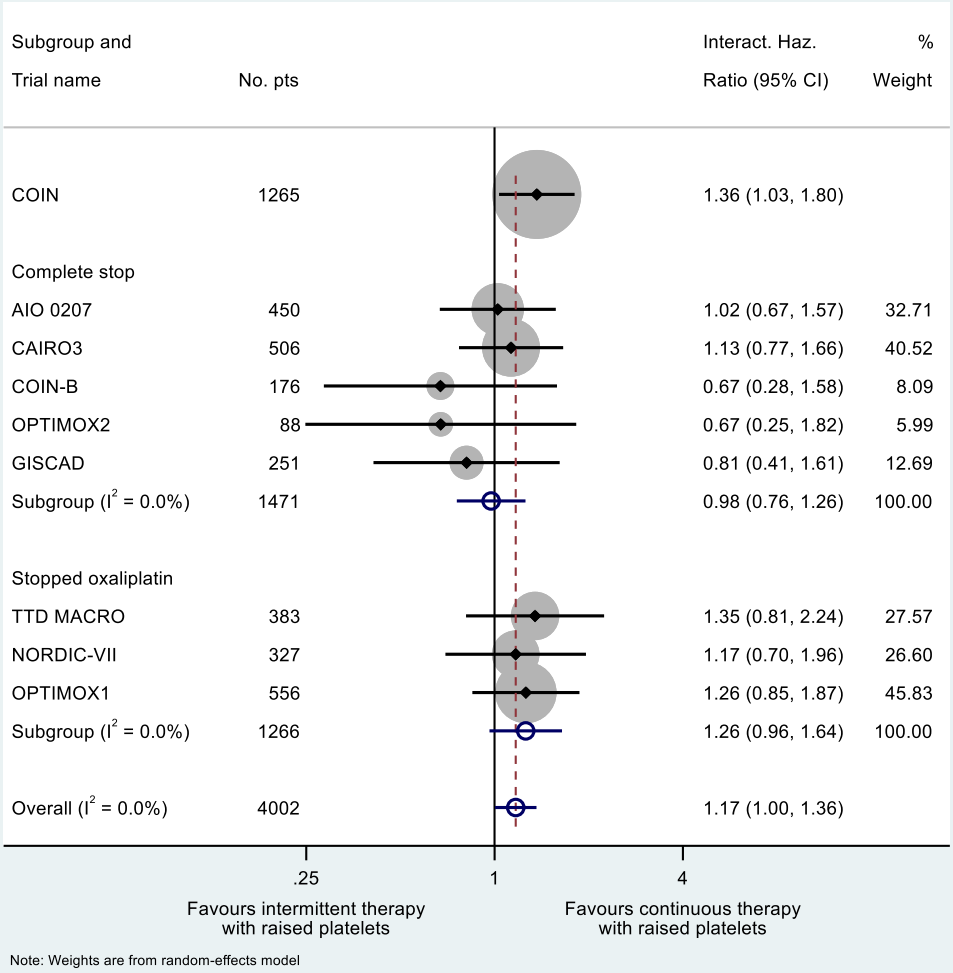


Supplementary Figure S6 – Interaction effect on OS between treatment strategy and platelet count as a continuous measurement

Note: Interaction HRs are interpretable as the change in the effect of intermittent versus continuous therapy for each increase of 100×10^9/l in platelet count.



Supplementary Figure S7 – PFS interaction effect between treatment strategy and thrombocytosis



Supplementary Figure S8 – Effect of intermittent versus continuous therapy on OS, with additional published results

Published results are only taken from trials which randomised at the *end* of induction therapy (see Table 1), to be comparable with the primary analysis of IPD. Relevant additional trials are: CR06B, SAKK 41/06, and Luo et al.