

RECONSIDERING THE BENEFIT OF INTERMITTENT VERSUS CONTINUOUS TREATMENT IN THE MAINTENANCE TREATMENT SETTING OF METASTATIC COLORECTAL CANCER

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SELECTED HIGHLIGHTS

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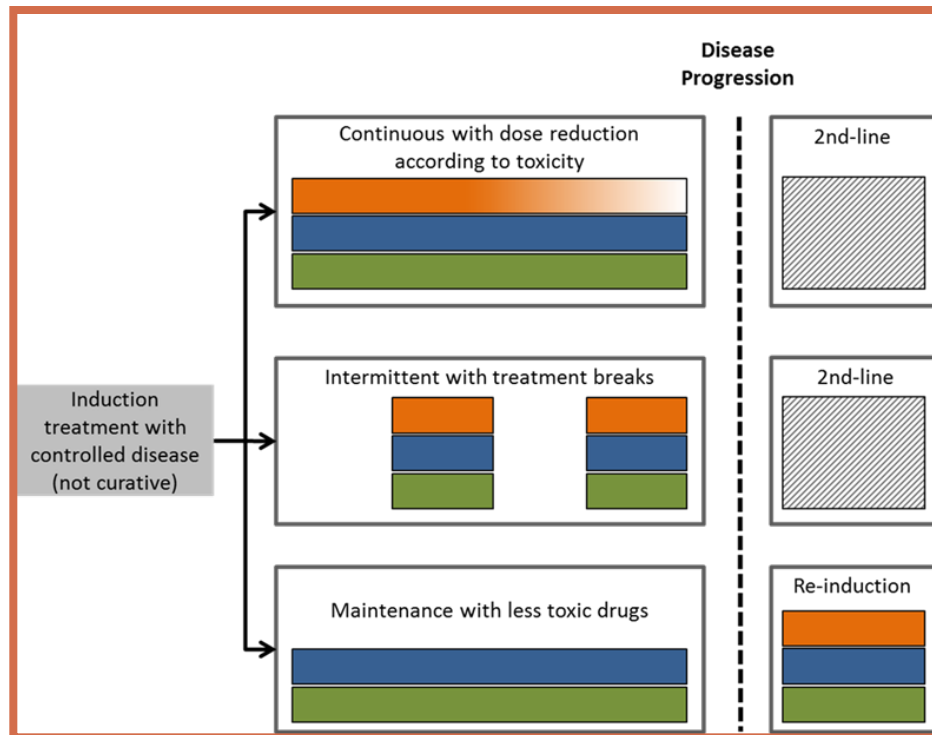
BACKGROUND (1)

- CRC is one of the most frequent solid tumours in the western world.¹
 - Survival rates are notably low in patients with metastatic disease
- The mainstay of standard first-line chemotherapy in the metastatic setting is doublet chemotherapy regimens such as FOLFOX or FOLFIRI.²⁻⁴
- Conventional first-line treatment involves continuous treatment until progression or intolerable toxicities, but only a third of patients are treated until progression, largely due to the side effects of chemotherapy.⁵⁻⁷
- Recent studies have investigated the clinical benefits of bevacizumab-based intermittent and continuous treatment regimens in the mCRC setting.

BACKGROUND (2)

- For patients that are suitable for intensive therapy, the optimal sequence and duration of chemotherapy is unknown, and reducing treatment intensity may be a clinical necessity.
- Various strategies are used to reduce the intensity of treatment:

Possible maintenance and holiday strategies evaluated in clinical trials



AIMS OF THIS REVIEW

The aims of this review were to reconsider the evidence for clinical benefit of **intermittent versus continuous treatment in the maintenance treatment setting of mCRC** and to evaluate the effect of ***RAS* and *BRAF* mutational status on maintenance strategies.**

INTERMITTENT TREATMENT STRATEGIES

- Several randomized phase III trials have evaluated intermittent treatment strategies in mCRC (in each study, oxaliplatin was withheld in the intermittent arm):

Trial	Induction regimen	Phase	Primary endpoint	Maintenance regimen	N	Median term of primary endpoint	HR (95%CI) P-value	Median OS	HR (95%CI) P-value
MRC CR06 ¹	5-FU/FA raltitrexed	III	2-year survival rate	5-FU/FA Raltitrexed	176	13%	NA P=0.23	11.3	0.87 P=0.87
				Chemo-free	178	19.5%		10.8	
OPTIMOX1 ²	FOLFOX	III	Superiority for duration of disease control*	Continuous	311	9.0*	0.99 (0.81-1.15) P=0.89	19.3*	0.93 (0.72-1.11) P=0.49
				FU+LV with intermittent oxaliplatin	309	10.6*		21.2*	
COIN ³	FOLFOX/ XELOX	III	Non-inferiority for OS* in ITT and PPS Limit HR; 1.162	Continuous	815 (ITT)	15.8*	1.084 (1.008-1.165)	-	-
				Intermittent FOLFOX/XELOX	815 (ITT)	14.4*		-	
				Continuous	467 (PPS)	19.6*	1.087 (0.986-1.198)	-	-
				Intermittent FOLFOX/XELOX	511 (PPS)	18.0*		-	

*From start of induction

INTERMITTENT TREATMENT STRATEGIES (CONT'D)

- Several randomized phase III trials have evaluated intermittent maintenance therapy in mCRC:

Trial	Induction regimen	Phase	Primary endpoint	Maintenance regimen	N	Median term of primary endpoint	HR (95%CI) P-value	Median OS	HR (95%CI) P-value
CONcePT ¹	FOLFOX +bev	III	Superiority for time to treatment failure	Continuous	Total 139	18 (week)	0.58 (0.41-0.83) P=0.0025	-	-
				FU+LV+bev with intermittent oxaliplatin		25 (week)		-	
GISCAD ²	FOLFIRI	III	Non-inferiority for OS	Continuous	146	17	0.88 (0.69-1.14)	-	-
				Intermittent FOLFIRI	147	18		-	

In each study, oxaliplatin was withheld in the intermittent arm

INTERMITTENT TREATMENT STRATEGIES (CONT'D)

- MRC CR06 compared intermittent vs continuous application of 5-fluorouracil + folinic acid (5-FU/FA) or raltitrexed in patients that did not progress during a 12 week induction period.¹
 - This study was powered to detect a 10% difference in 2 year survival rate and was not able to show any difference in OS (HR 0.87).
- The remaining studies aimed to address cumulative oxaliplatin toxicity with oxaliplatin being withheld in the intermittent arm.
- Patients randomized to the 'stop and go' strategy in OPTIMOX1 received 6 cycles of intensified FOLFOX7 followed by 12 cycles of maintenance fluorouracil/leucovorin without oxaliplatin, followed by reintroduction of FOLFOX7 for another 6 cycles.²
 - The control group received FOLFOX4 continuously until unacceptable toxicity or progression
- The intermittent arm in the CONcept trial maintained fluorouracil/leucovorin (plus bevacizumab) with intermittent oxaliplatin³, whereas in the COIN trial, all drugs in the intermittent arm were given on a 12-weeks-on, 12-weeks-off schedule.⁴
- Results from these three studies suggest that a partial 'stop and go' strategy is feasible and better tolerated than continuous chemotherapy with oxaliplatin.

CONTINUOUS MAINTENANCE TREATMENT

- Several randomized phase III trials have evaluated continuous maintenance therapy in mCRC:

Trial	Induction regimen	Phase	Primary endpoint	Maintenance regimen	N	Median term of primary endpoint	HR (95%CI) P-value	Median OS	HR (95%CI) P-value
OPTIMOX2 ¹	FOLFOX	III	Superiority for duration of disease control*	FU+LV	98	13.1*	0.71 (0.51-0.99) P=0.046	23.8	0.88 P=0.42
				Chemo free	104	9.2*		19.5	
CAIRO3 ²	CAPOX+bev	III	Superiority for TFS	capecitabine +bev	278	11.7	0.67 (0.56-0.81) P<0.0001	21.6	0.89 (0.73-1.07) P=0.22
				Chemo free	279	8.5		18.1	
AIO KRK-0207 ³	FP +oxaliplatin +bev	III	Non-inferiority for TFS Limit HR; 1.43	FP+bev	158	6.9	1.26 (0.99-1.60) P=0.056	23.8	-
				Chemo free	158	6.4		23.1	
SAKK 41/06 ⁴	Various regimens +bev	III	Non-inferiority for time to progression* Limit HR; 0.727	bev alone	131	4.1	0.74 (0.58-0.96)	25.4	0.83 (0.63-1.1) P=0.2

*From start of induction

CONTINUOUS MAINTENANCE TREATMENT (CONT'D)

OPTIMOX2 study:¹

- Maintenance therapy with intermittent oxaliplatin demonstrated an advantage over a full treatment break, with significant improvements in the duration of disease control and median PFS, but not OS.

CAIRO3 study:²

- Maintenance with capecitabine + bevacizumab was well tolerated and superior to no treatment in terms of PFS, but there was no significant effect on OS.²

AIO KRK-0207 study:³

- Median time to failure of strategy was 6.9 months for maintenance with fluoropyrimidine + bevacizumab versus 6.1 months with bevacizumab alone, and 6.4 months in the no treatment group.³
- A maintenance concept of fluoropyrimidine + bevacizumab demonstrated significantly longer PFS from the start of maintenance versus bevacizumab monotherapy or drug holiday.

SAKK 41/06 study:⁴

- Non-inferiority was not demonstrated for treatment holidays versus bevacizumab monotherapy as maintenance treatment.⁴
- There was no impact on OS.
- The authors concluded that single-agent bevacizumab had no meaningful therapeutic value with this treatment approach.

OPTIMIZING MAINTENANCE THERAPY

- Several randomized phase III trials have evaluated improved regimens for continuous maintenance treatment:

Trial	Induction regimen	Phase	Primary endpoint	Maintenance regimen	N	Median term of primary endpoint	HR (95%CI) P-value	Median OS	HR (95%CI) P-value
MACRO ¹	XELOX+bev	III	Non-inferiority for PFS* Limit HR; 1.32	Continuous	239	10.4*	1.1 (0.89-1.35) P=0.38	23.2*	1.05 (0.85-1.30) P=0.65
				Bev alone	241	9.7*		20.0*	
AIO KRK-0207 ²	FP +oxaliplatin +bev	III	Non-inferiority for TFS Limit HR; 1.43	FP+bev	158	6.9	1.08 (0.85-1.37) P=0.53	20.2	-
				Bev alone	156	6.1		21.9	
Turkish Oncology Group Trial ³	XELOX+bev	III	Superiority for PFS*	Continuous	62	8.3*	0.6 P=0.002	20.2*	P=0.10
				capecitabine +bev	61	11.0*		23.8*	

*From start of induction treatment

OPTIMIZING MAINTENANCE THERAPY (CONT'D)

- Several randomized phase III trials have evaluated improved regimens for continuous maintenance treatment:

Trial	Induction regimen	Phase	Primary endpoint	Maintenance regimen	N	Median term of primary endpoint	HR (95%CI) P-value	Median OS	HR (95%CI) P-value
DREAM ¹	Various regimens +bev	III	Superiority for PFS	bev+erlotinib	224	5.9	0.77 (0.62-0.94) P=0.012	24.9	0.79 (0.64-0.98) P=0.035
				bev alone	228	4.9		22.1	
Nordic ACT/ ACT-1 ²	XELOX/ XELIRI or FOLFOX/ FOLFIRI +bev	III	Superiority for PFS	bev+erlotinib	82	5.7	0.79 (0.55-1.12) P=0.19	21.5	0.88 (0.61-1.27) P=0.51
				bev alone	80	4.2		22.8	

MAINTENANCE THERAPY WITH ANTI-EGFR ANTIBODIES

Two phase II studies have evaluated maintenance therapy with anti-EGFR antibodies in patients with *KRAS* wild-type metastatic colorectal cancer:

1.COIN-B:¹

- An exploratory phase II study that investigated the addition of cetuximab to intermittent FOLFOX which included a prospectively selected *KRAS* wild-type population.
- Following 12 weeks of FOLFOX + weekly cetuximab, patients were randomised to continuous weekly cetuximab or to no treatment until disease progression (at which time FOLFOX plus cetuximab was reinitiated).
- Among 130 patients, median failure-free survival and OS were 12.2 months and 16.8 months, respectively, in the intermittent group and 14.3 months and 22.2 months, respectively, in the continuous cetuximab group.

2.In the second phase II study, weekly cetuximab monotherapy was found to be non-inferior to continued FOLFOX plus cetuximab when given as maintenance therapy in wild-type *KRAS* metastatic colorectal cancer.²

FUTURE DEVELOPMENTS IN MAINTENANCE THERAPY

Aflibercept and regorafenib, are being investigated in the maintenance setting:

- **Aflibercept** is being evaluated as single-agent maintenance therapy following induction with first-line XELOX plus aflibercept in an Italian phase I/II trial (AMOR trial; NCT01955629).
- An ongoing placebo-controlled phase III study is evaluating **regorafenib** as maintenance therapy in *KRAS* and *NRAS* wild-type metastatic colorectal cancer (RAVELLO trial; EudraCT: 2013-005428-41).¹

MGN1703, a synthetic immunomodulator that acts as a Toll-like receptor (TLR)-9 agonist, has also been investigated as maintenance treatment for mCRC:

- The randomised, placebo-controlled phase II IMPACT study evaluated MGN1703 vs placebo as maintenance therapy after first-line treatment.
- Median PFS was longer in the MGN1703 arm (2.8 months with MGN1703 versus 2.6 months with placebo).²
- An ongoing phase III study, IMPALA, is evaluating single-agent MGN1703 as maintenance therapy versus usual maintenance therapy (NCT02077868).³

WHEN SHOULD MAINTENANCE THERAPY BE INITIATED?

- There is considerable variation in the duration of induction chemotherapy prior to initiation of maintenance treatment (or drug-free interval), ranging from 2 to 6 months in the GISCAD, COIN, OPTIMOX and AIO KRK-0207 trials.¹⁻⁵
- The timing of maintenance therapy depends on the efficacy of the induction regimen.⁶
- Newer tumour dynamic measurements based on individualized patient measurements may help to define the optimal point to stop induction therapy (e.g. early-tumor-shrinkage and depth of response).^{7,8}
- The perfect candidate for an early maintenance switch, is a patient whose tumor has responded well after 6-8 weeks of induction and is stable in the next assessment.
- A patient whose tumor is stable as the best response may need a longer induction period.
- The presence of mutations such as *BRAF* and *RAS* should also be considered when deciding when to initiate maintenance therapy in the light of their prognostic value on overall survival.

INDIVIDUALISED TREATMENT IN THE MAINTENANCE SETTING

- Maintenance treatment needs to be individualised based on patient, tumour, and treatment characteristics, as well as molecular biomarkers.
- Several studies and analyses have examined the role of such factors in predicting clinical benefit in the maintenance setting including the CAIRO3, AIO KRK-0207, OPTIMOX, COIN studies.¹⁻⁵
- Results from these studies suggest that factors associated with response to initial therapy and patient characteristics at baseline may serve as biomarkers to identify patients who may have significantly impaired survival with an intermittent treatment strategy.

INDIVIDUALISED TREATMENT IN THE MAINTENANCE SETTING (CONT'D)

Data are lacking regarding the relationship between maintenance strategies and mutation status, particularly for patients with *RAS* and *BRAF* mutations that confer a worse prognosis.

The prognostic impact of mutation status was evaluated in the AIO KRK-0207 study and an accompanying subgroup analysis by Hegewisch-Becker, et al.^{1,2}

- In a subgroup analysis, *KRAS/NRAS* (exons 2, 3 and 4) and *BRAF* V600E mutations were prognostic for PFS ($P=0.014$) and OS ($P<.0001$) in the entire patient cohort.
- Median OS was 30.2, 23.4 and 9.4 months for patients with wild-type, *KRAS/NRAS* mutant and *BRAF* mutant disease, respectively.²
- There was also a significant interaction between mutation status and maintenance therapy for time to first progression.
- In patients with wild-type disease, bevacizumab was superior to no treatment, with a median PFS of 6.8 and 3.9 months, respectively ($P<.001$). However, bevacizumab was not superior to no treatment among patients with any mutation (median PFS, 4.2 versus 3.6 months, respectively; $P=0.17$).²
- Maintenance with bevacizumab monotherapy appeared comparable to fluoropyrimidine plus bevacizumab in wild-type patients (median PFS of 6.8 vs 7.3 months, respectively), whereas combined treatment was beneficial in patients with any mutation (median PFS of 6.4 versus 3.6 months, respectively)²
- In contrast to the results for PFS, results for OS showed no association between mutation status and maintenance therapy²

CONCLUSIONS

- After a successful induction treatment with doublet chemotherapy, fluoropyrimidine plus bevacizumab is a safe and easy to use maintenance strategy.
- A drug holiday is an option that should be discussed with patients that do not have a *BRAF* mutant tumour, as no negative effect with regard to OS has been proven in these patients.
- Further molecular sub-classification of CRC cases may help to further individualise patient treatment with regard to the ideal induction and maintenance strategy.