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SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

# Current Status of Maintenance Systemic Therapies in Metastatic Colorectal Cancer: 2018 Update

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## Abstract

**Purpose of Review** Current systemic management of MCRC includes periods of intensive induction treatment followed by surgery and/or local ablation or maintenance or complete stop. This article is an update of the 2017 review by Quidde et al. and evaluates the most recent data on maintenance strategies in MCRC.

**Recent Findings** Induction followed by maintenance and if feasible re-induction treatment does not seem to be inferior to continuous full-dose treatment for patients with MCRC responding to first-line combination regimen but without options for secondary resection or local ablation. Active maintenance seems to be superior to complete stop after at least 3 months of induction treatment in terms of progression-free survival and may add some benefit in terms of OS. The addition of PD-L1 inhibition to maintenance was not effective. The choice of the respective maintenance strategy may be personalised taking into account disease and patient characteristic, choice of induction treatment and response, treatment tolerability and quality of life.

**Summary** Patients with MCRC and no options of secondary resection or local ablation should be considered for maintenance treatment.

**Keywords** Metastatic colorectal cancer · Personalised · Induction · Maintenance

## Introduction

Colorectal cancer is one of the most common cancers and one of the leading causes of cancer death worldwide [1, 2]. At time of diagnosis, around one quarter of patients with CRC present synchronous metastases and another at least 30% of patients will develop metastases during treatment, resulting in a high overall mortality rate [3].

The armamentarium of systemic therapy (fluoropyrimidines (5FU, capecitabine), irinotecan, oxaliplatin, trifluridine/tipiracil, monoclonal antibodies against VEGF (bevacizumab), VEGFR2 (ramucirumab) and EGFR (cetuximab, panitumumab), as well as anti-angiogenic receptor fusion proteins (aflibercept) and tyrosine kinase inhibitors (regorafenib)) and of local approaches (surgery, radiofrequency or microwave ablation, radio- or chemoembolization or radiotherapy) remained unchanged during the last years [4•]. New agents, e.g. checkpoint inhibitors, are still evaluated in clinical trials but are currently no standard in the treatment of metastatic CRC (MCRC), beside patients with metastatic microsatellite instable (MSI-high) or deficient mismatch repair (dMMR) tumours [5–7]. For further molecular defined patient populations, targeted treatments are available, although not reimbursed everywhere, e.g. vemurafenib in combination with cetuximab in BRAF mutated or trastuzumab and lapatinib or pertuzumab, in human epidermal growth factor receptor 2 (HER2)-positive MCRC [8–10].

Current first-line regimens are either doublet or triplet chemotherapy combinations with 5FU/leucovorin (LV) and irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) or both (FOLFOXIRI) in combination with EGFR antibodies (only for RAS/BRAF wild-type tumours) or bevacizumab. These highly active regimens induce relevant tumour shrinkage in 40 to 65% of patients and result in significantly prolonged progression-free survival (PFS) of 10–12 months [11–15].

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The median treatment duration is about 5–6 months with only few patients receiving full-dose treatment until progression.

Several approaches (Table 1) are available conducting long-term chemotherapy in MCRC patients, including full treatment continuation until progression, on-off approaches or maintenance either as de-escalation or even "escalation" with switch maintenance or complete stop of treatment after 3–6 months of chemotherapy.

This article is an update of "Personalizing Maintenance Therapy in Metastatic Colorectal Cancer. *Current Colorectal Cancer Reports,* 2017"[16] reviewing the most recent data on maintenance strategies through October 2018.

## Stop-and-Go Maintenance Approaches in the Chemotherapy-Alone Setting

Historically, the first generation of trials evaluated stop-and-go approaches in a chemotherapy-alone setting compared to continuation of full-dose chemotherapy until progression. Of note, these trials applied non-contemporary induction regimen, e.g. with single-agent fluoropyrimidines or a doublet chemotherapy (fluoropyrimidines and oxaliplatin or irinotecan), without antibodies or a third chemotherapeutic drug.

The MRC CR06 was one of the first trials evaluating a stop-and-go with restart at progression strategy in 354 MCRC patients [17]. After 3 months of single-agent fluoropyrimidine or raltitrexed, patients with at least stable disease were randomised to either intermittent (complete stop of chemotherapy and re-start on the same drug on progression) or continuous chemotherapy until progression. OS was not different in both groups, but numerically favouring intermittent treatment (HR 0.87 numerically favouring intermittent, 95% CI 0.69–1.09, $p = 0.23$). Intermittent compared to continuous chemotherapy resulted in significantly fewer toxic effects and serious adverse. Similarly, but with a more intensive induction regimen (FOLFOX/CAPOX), the COIN trial evaluated a complete stop of oxaliplatin-based chemotherapy after 3 months (arm C, $n = 815$ patients) compared to continuous oxaliplatin-based chemotherapy (arm A, $n = 815$ patients) [18]. Comparing arms A and C median, OS was 15.8 and 14.4 (HR 1.084) in the intent-to-treat population and 19.6 and 18.0 months in the per protocol population (HR 1.087), respectively. The upper limits of the confidence intervals were greater than the predefined non-inferiority boundaries, thus non-inferiority could not be demonstrated. More patients on continuous than on intermittent treatment had grade 3 or worse haematological toxic effects, peripheral neuropathy and hand-foot syndrome.

Two further trials evaluated strategies with pre-planned intervals and either complete stop or maintenance with 5FU/LV. The OPTIMOX1 trial randomised 620 patients with MCRC to FOLFOX administered continuously until progression (arm A) or FOLFOX for 3 months followed by maintenance with 5FU/LV for 6 months, and reintroduction of FOLFOX thereafter (arm B) [19]. Median PFS and OS were not significantly different in both arms (PFS arm A/B was 9.0/8.7 months, HR 1.06; 95% CI, 0.89–1.20; $p = 0.47$; OS arm A/B was 19.3/21.2 months, HR 0.93; 95% CI, 0.72–1.11; $p = 0.49$). The risk of developing a grade 3 to 4 toxicity was relevantly reduced during maintenance with 5FU/LV without oxaliplatin in arm B. The GISCAD trial showed similar results for an irinotecan-based regimen in 337 MCRC patients [20]. The intermittent chemotherapy with 5FU/LV and irinotecan 2 months on/2 months off (arm A) was as effective as the same regimen given continuously (arm B) in terms of OS (median 18 vs. 17 months for arm A and B, HR 0.88), PFS (6 months in both, HR 1.03) and grade 3–4 toxicity in totality. The median chemotherapy-free period (drug holiday) in arm A was 3.5 months.

**Table 1** Maintenance approaches

| Continuous | Stop-and-go approach | | | |
|---|---|---|---|---|
| | Partial stop-and-go with maintenance | | Complete stop-and-go | |
| Continue until progression or unacceptable toxicity | Restart at progression<br>•Stop most toxic drug (e.g. oxaliplatin)<br>•Continue only 5FU or bevacizumab or 5FU in combination with bevacizumab or anti-EGFR until progression<br>• Restart drug at progression | Pre-planned intervals<br>Stop/restart toxic drugs in pre-planned intervals (3/4 months on/off) | Restart at progression<br>• Stop all drugs<br>• Restart at progression<br>• Stop after further 3 months | Pre-planned intervals<br>Stop/restart all drugs in pre-planned intervals |

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Based on these results, intermittent treatment with single-agent or doublet chemotherapy and either full stop or 5FU/LV maintenance could reduce toxicity without effecting OS negatively. Based on the comparison to full-dose chemotherapy until progression, the differential effect of either complete stop or less-intensity maintenance remained unclear. Thus, the OPTIMOX 2 trial compared a maintenance treatment with 5FU/LV (arm A = maintenance arm) to full stop of chemotherapy (arm B), both after 6 cycles of FOLFOX and re-induction of FOLFOX in case of progression in 202 patients [21]. The planned complete discontinuation of chemotherapy had a negative impact on the duration of disease control (DDC; median DDC was 13.1 and 9.2 months in patients assigned to arm A and B; $p = 0.046$) and PFS (8.6 and 6.6 months for arm A and B, $p = 0.0017$) but not on OS. The results add to personalising treatment in the maintenance setting, indicating that active maintenance should be chosen if disease control is the focus.

## Stop-and-Go Maintenance Approaches with Chemotherapy and Antibodies

Upon inclusion of monoclonal antibodies into the first-line treatment of MCRC, maintenance approaches were adapted accordingly and maintenance approaches with restart at progression or in pre-planned intervals compared to continuation of full-dose chemotherapy and monoclonal antibodies.

In the MACRO trial, 480 MCRC patients got induction treatment with capecitabine, oxaliplatin (CAPOX) and bevacizumab. After 4.5 months, one group continued treatment CAPOX and bevacizumab, the other group got bevacizumab [22]. Median PFS and OS were in the same range, but the maintenance treatment was associated with significantly less polyneuropathy, hand-foot syndrome and fatigue compared to the continuous group. In a similarly designed Turkish trial, the intensified maintenance strategy with capecitabine and bevacizumab after 4.5 months of CAPOX and bevacizumab was compared to continuation of full treatment in 123 patients [23]. Likely based on the longer median treatment duration of 8 vs. 11 cycles, PFS was significantly increased (8.3 vs. 11 months, HR 0.60; $p = 0.002$) by the maintenance regimen. In the CONCEPT trial, 139 MCRC patients were randomised to FOLFOX and bevacizumab either continuously or intermittently with 5FU/LV and bevacizumab maintenance with pre-planned intervals every 8 cycles. Median time to treatment failure (time from randomisation to discontinuation of treatment for any reason) was significantly better for the intermittent arm with 25 weeks compared to 18 weeks in the continuous arm (HR = 0.58; 95% CI 0.41–0.83; $p = 0.0025$) [24]. Data on EGFR antibodies are rare in this setting and limited to single arm studies. Thus, the NORDIC-7.5 trial evaluated the impact of cetuximab maintenance after 8 cycles of FLOX and cetuximab induction treatment. Median PFS and OS were 8.0 (95% CI 7.5–8.9) and 23.2 months (95% CI 18.1–27.4) and thus similar to the results of the FLOX and cetuximab arm in the NORDIC VII trial [25, 26].

These clinical trials showed no relevant detriment of a maintenance or complete stop strategy compared to continuous full-dose treatment, after induction treatment. The next trial generation compared the intensity of maintenance strategies (nothing vs. single agent vs. combination) after 3–6 months of induction treatment either bevacizumab or anti-EGFR based.

## Bevacizumab-Based Maintenance Strategies

The largest dataset is available for bevacizumab-based maintenance strategies with more than 1000 patients randomised in four large trials (CAIRO 3, SAKK 41/06, AIO KRK 0207, PRODIGE 9) [27, 28, 29, 30].

In the CAIRO 3 trial, 558 patients were randomised to either maintenance treatment with metronomic low dose capecitabine and bevacizumab (maintenance) or observation alone after 6 cycles of CAPOX and bevacizumab (4.5 months). Median PFS2 was significantly improved in patients on maintenance treatment, and was 8.5 months in the observation group and 11.7 months in the maintenance group (HR 0.67; 95% CI 0·56–0·81, $p < 0·0001$). Besides more hand-foot syndrome (23%), the maintenance treatment was well tolerated and quality of life was clinically not different between treatment groups [27].

Low intensity maintenance with single-agent bevacizumab was evaluated in the SAKK 41/06 trial [28]. Overall, 262 patients without disease progression 4–6 months after induction treatment with a fluoropyrimidine, alone (6%) or in combination with irinotecan (32%) or oxaliplatin (62%), and bevacizumab were randomly assigned to continuation of bevacizumab or observation alone. Median time to progression (TTP) was 4.1 months for bevacizumab continuation versus 2.9 months for treatment break (HR 0.74; 95% CI 0.58–0.96). The median overall survival was 25.4 months for bevacizumab continuation versus 23.8 months (HR 0.83; 95% CI 0.63–1.1; $p = 0.2$) for observation alone. In the PRODIGE 9 trial, 491 MCRC patients were randomly assigned to maintenance treatment with bevacizumab or observation alone after 12 cycles of fluorouracil, leucovorin, irinotecan and bevacizumab (6 months). The primary endpoint tumour control duration was 15 months in both arms. Chemotherapy-free intervals were similar between both arms (4.3 months). Median PFS and OS were 8.9 and 22.0 months for observation alone vs. 9.2 and 21.7 months for bevacizumab maintenance, respectively (HR 0.91; 95% CI 0.76–1.09; $p = 0.316$ and HR 1.07; 95% CI 0.88–1.29, $p = 0.5$).

In the AIO KRK 0207 trial, after 24 weeks of induction therapy with any fluoropyrimidine, oxaliplatin and bevacizumab, 472 patients without disease progression were randomised to maintenance treatment with a fluoropyrimidine plus bevacizumab (arm A), bevacizumab alone (arm B), or observation (arm C) [29]. PFS1 (secondary endpoint) from randomisation was 6.3, 4.6 and 3.5 months for arm A, B and C, respectively. Bevacizumab alone was non-inferior to standard fluoropyrimidine plus bevacizumab (HR 1.08; 95% CI 0.85–1.37; upper limit of the one-sided 99.8% CI 1.42), whereas observation alone was not non-inferior (HR 1.26; 95% CI 0.99–1.60; upper limit of the one-sided 99.8% CI 1.65).

Available meta-analyses of the first three bevacizumab-based trials (CAIRO 3, SAKK 41/06, AIO KRK 0207) showed significant prolonged PFS1 (HR 0.40; 95% CI 0.34–0.47) and PFS2 (HR 0.70; 95% 0.60–0.81), and a trend towards prolonged OS (HR 0.91; 95% CI 0.78–1.05) when compared to complete stop [31]. The indirect comparison of the more intensive maintenance (bevacizumab and fluoropyrimidine) and bevacizumab alone showed an improved PFS (HR 0.63, 95% CI 0.50–0.79) with the combination strategy. There was no impact on OS favouring one of these two maintenance strategies (HR 1.08, 95% CI 0.82–1.42) [32]. However, none of these meta-analyses included the French trial with a very moderate impact on PFS (HR 0.91) [30].

## EGFR Antibody–Based Maintenance Strategies

In the COIN-B trial, 169 KRAS wild-type patients were randomised to treatment stop or cetuximab maintenance, both until disease progression after 12 cycles of FOLFOX and cetuximab. The median failure-free survival was 12.2 months (95% CI 8.8–15.6) and 14.3 months (10.7–20.4), for the intermittent and continuous cetuximab arm respectively [33]. The MACRO 2 trial assessed FOLFOX and cetuximab maintenance vs. cetuximab single agent after 4 months FOLFOX and cetuximab in 193 RAS wild-type MCRC patients showing no difference in PFS (HR 1.19; 95% CI 0.8–1.79) or OS (HR 1.24; 95% CI 0.85–1.79) for cetuximab vs. the full-dose treatment [34]. In the recently presented VALENTINO trial, 229 RAS wild-type MCRC patients were randomised after 4 months first-line treatment with FOLFOX and panitumumab to FU/FA plus panitumumab (arm A) or panitumumab alone (arm B). In terms of PFS panitumumab alone (10.2 months) was likely inferior to FU/FA plus panitumumab (13.0 months) (HR 1.55; 95% CI 1.09–2.2; $p = 0.011$), thus favouring the combination arm [35].

## Switch Maintenance or Inserting New Agents in the Maintenance Setting

### Erlotinib

In the DREAM/OPTIMOX 3 trial, maintenance therapy with bevacizumab and erlotinib showed a trend towards improved PFS (HR 0.81; 95% CI 0.66–1.01; $p = 0.059$) and significantly improved OS (HR 0.79; 95% CI 0.63–0.99; $p = 0.036$) compared to bevacizumab alone after induction treatment with fluoropyrimidine and oxaliplatin or irinotecan and bevacizumab [36]. In the Nordic ACT Trial, MCRC patients got 18 weeks induction chemotherapy plus bevacizumab and were randomised to bevacizumab and erlotinib (arm A) or bevacizumab (arm B) maintenance [37]. A non-significant favourable trend in median PFS was noted for the more intensive maintenance (5.7 and 4.2 months for arm A and B), but significant more toxicity like rash, diarrhoea and fatigue was noted in arm A compared to arm B. Therefore, the licencing and consecutive administration of erlotinib in the MCRC maintenance setting seems to be unlikely.

### Atezolizumab

The MODUL trial evaluates different novel regimen in molecularly selected cohorts in MCRC (e.g. BRAF mutant or HER2 positive) after 3–4 months induction treatment with FOLFOX and bevacizumab [38]. In the 2nd cohort of the trial, patients without a specific molecular profile amenable for targeted treatment and with at least stable disease ($n = 445$) were randomised in a 2:1 ratio to maintenance treatment with fluoropyrimidine and bevacizumab with or without atezolizumab. No improvement in median PFS (7.2 vs. 7.39 months, HR 0.96; 95% CI 0.77–1.22, $p = 0.727$) or median OS (22.05 vs. 21.91 months, HR 0.86; 95% CI 0.66–1.13, $p = 0.283$) was seen for the addition of atezolizumab [39]. Diarrhoea, arthralgia and immune side effects were more often in the atezolizumab maintenance regime.

## Future Perspectives

In general trials like the MODUL trial, evaluating different maintenance approaches in molecularly selected patient populations, e.g. BRAF mutated or HER2 positive, after a standard induction treatment is the ideal platform for innovative maintenance strategies, although the main challenge remains, what to apply in the large group of patients without targetable alterations (about 90% of patients with MCRC) [38]. Furthermore, it might be useful to conduct these trials by an academic group with access to different agents from several companies.

Regarding the most recent data on immunotherapy combinations in MCRC (e.g. for cobimetinib and atezolizumab or atezolizumab in addition to fluoropyrimidine and bevacizumab), currently no immunotherapy combinations have shown the potential to be evaluated in a larger randomised trial in the maintenance setting [39, 40]. The eagerly awaited results from the IMPALA trial, evaluating the effects of an immunomodulation with toll-like receptor 9 agonist (MGN1703) after conventional induction chemotherapy in a phase 3 setting after the positive results of a small randomised trial, might establish a further agent in this setting amenable for future combination approaches [41].

## Personalising Maintenance

In the CAIRO 3 trial, a significant interaction between response to induction treatment (complete or partial response vs. stable disease) and maintenance for OS was noted. Whereas, OS was 18.8 vs. 24.1 months in complete or partial responders ($n = 366$), in stable disease patients ($n = 191$) the OS was only 15.2 vs. 16.9 months, for observation vs. maintenance respectively [27]. In AIO 0207, the same retrospective subgroup analyses were performed for PFS without a significant effect of response to induction treatment on fluoropyrimidine and bevacizumab maintenance [29]. Despite the clear rationale with a better chemo-sensitivity and thus higher likelihood of benefit, clinical data are not yet clear on this issue.

In the CAIRO 3 study, an interaction was noted for KRAS mutational status with PFS2 and OS. In KRAS wild-type patients, maintenance compared to observation alone significantly improved OS (HR 0.64; 95% CI 0.47–0.87), whereas no difference was noted in KRAS-mutated patients (HR 1.07; 95% CI 0.77–1.84) [42]. For PFS2, the beneficial impact of maintenance was reduced in KRAS-mutated patients (HR 0.72) compared to KRAS wild-type (HR 0.45). In the AIO 0207 trial, the beneficial impact of maintenance on PFS seemed to be less in RAS or BRAF mutated patients compared to RAS/BRAF wild-type patients, particularly for single-agent bevacizumab [29].

Localization of primary tumour (LPT) as a prognostic and predictive value in MCRC influences treatment decisions for induction treatment. Several trials showed no benefit using EGFR antibodies in RAS wild-type patients with right-sided MCRC in comparison to left-sided MCRC. To date, information about the predictive value of tumour localization on different maintenance strategies is limited. The AIO 0207 trial analysed PFS and OS on maintenance therapy according to tumour localization and mutational subgroups (BRAF/RAS) and demonstrated that there was no predictive impact of tumour localization on the maintenance strategies. The pairwise comparison of treatment arms showed a better PFS for FU/Bev versus no treatment independent from tumour localization (left, $p < .0001$; HR, 2.39; 95% CI, 1.73–3.31; right, $p = .011$; HR, 1.78; 95% CI, 1.14–2.80). Analysis for OS (429 patients) confirmed the strong prognostic impact of LPT (left vs. right, 24.0 vs. 16.7 months; $p < .0001$; HR, 1.65; 95% CI, 1.32–2.06), but again without major interaction between the LPT and maintenance arms [43].

## Discussion

The topic of maintenance treatment is still a matter of debate. Although a large variety of trials showed a positive benefit on PFS, the impact of maintenance treatment on OS remains unclear. Based on the different design and endpoints, the available trials are difficult to compare and/or to evaluate in a meta-analysis.

In summary, the available data show that maintenance treatment after intensive induction treatment is feasible and can be recommended particular to those patients who are not amenable for secondary resection or local ablation to reduce toxicity, to stabilise quality of life and to improve PFS. The combination of induction periods with intensive treatment followed by well-tolerated maintenance periods is of utmost importance in regard to a median OS of up to 30 months [16].

Recent data have shown that single-agent bevacizumab maintenance seems to have only very modest efficacy and thus a combination regimen with fluoropyrimidine might be the better choice if active maintenance is chosen [30]. Similarly, patients after anti-EGFR-based induction relevantly benefit from the combination approach (panitumumab with fluoropyrimidine), rather than single-agent panitumumab [35]. A potential treatment approach focusing on maximisation of first-line PFS is displayed in Fig. 1, although in terms of overall survival, complete treatment break still seems to be an alternative.

The addition of checkpoint inhibitors (atezolizumab) to fluoropyrimidine and bevacizumab maintenance showed no impact on PFS or OS but more side effects [38]. These data clearly challenge the use of PD-1/L1 inhibitors in a non-MSI-high/dMMR population as well as the further intensification of fluoropyrimidine and bevacizumab maintenance. Regarding the recent negative data on other immunotherapy combinations in the general MCRC population, current research rather focus on upfront combination regimen including checkpoint-inhibitors than on immunotherapy combinations only in the maintenance setting [40, 44]. Ongoing trials, e.g. on immunomodulation with MGN 1703, might reflate the evaluation of immunotherapies as maintenance regimen. Generally, a multi-agent platform approach with molecularly stratified maintenance regimen still seems to be the ideal strategy to establish new treatment approaches in the maintenance setting and beyond.

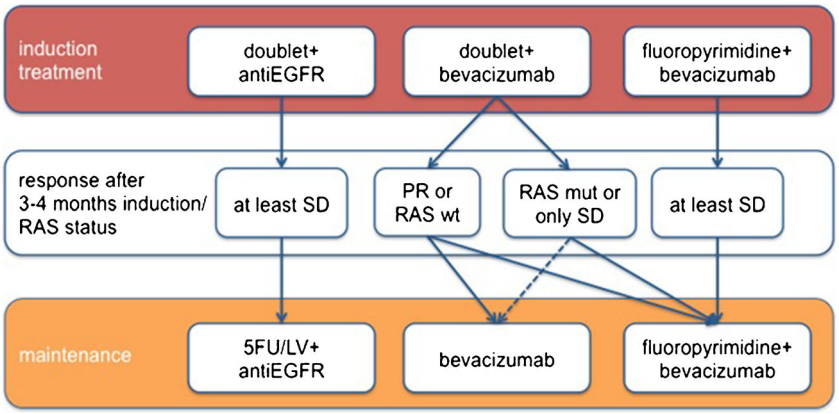


**Fig. 1** Possible maintenance approach to maximise progression-free survival 1 (until first progression)

Established prognostic factors (e.g. chemo sensitivity, primary tumour location, RAS/BRAF status or synchronous metastasis) may have an influence on the efficacy of active maintenance, but available retrospective clinical data are inconclusive. Notably, choice of maintenance treatment intensity has no negative impact on quality of life, and the application of maintenance compared to treatment break rather leads to a stabilisation of the quality of life [45•].

Based on the available data, current guidelines and expert recommendations include maintenance treatment as an important part of the whole MCRC treatment, rather than recommending combination maintenance regimen [4, 46•].

However, individual treatment tolerability is of high relevance and will be a major reason for decisions on maintenance strategy. The administration of maintenance treatment compared to complete stop should be a shared decision process taking into account disease and patients' characteristics, response to induction treatment, treatment tolerability, patient preference and quality of life.

## Conclusion

The intensity of systemic treatment of MCRC should be adapted to the respective tumour situation and include periods of intensive and less intensive treatment or even complete stop. Based on a recent data, a combination regimen should be applied if an active maintenance strategy is chosen. The choice of the respective strategy should take into account disease and patients' characteristic, choice of induction treatment and response, treatment tolerability, patient preference and quality of life in a shared decision process.

### Compliance with Ethical Standards

**Conflict of Interest** Julia Mann declares that she has no conflict of interest.

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