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REVIEW

Chemotherapy, Still an Option in the Twenty-First Century in Metastatic Colorectal Cancer?

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Abstract Substantial improvements have been made in the systemic treatment of colorectal cancer over the last two decades. Median overall survival (OS) of patients with metastatic colorectal cancer (mCRC) has been constantly increased and the most recent first-line studies exceeded the 30-month median overall survival. The standard first-line regimen for mCRC is a combination of chemotherapy plus a biological agent either targeting the main angiogenic growth factor vascular endothelial growth factor (VEGF) via Bevacizumab or by antibodies targeting the epidermal growth factor receptor (EGRF) via Panitumumab or Cetuximab. Recent improvements have been shown in the efficacy of the biological agent by stratifying these agents according to the primary tumor location. In this context EGFR-inhibitors showed improved OS when used first-line in tumors derived from the left-sided colon or rectum, while tumor sidedness was not predictive for anti-VEGF-antibodies. Furthermore, the biological activity of anti-EGFR antibodies is restricted to tumors with a rat sarcoma virus (RAS)-wild-type genotype but not RAS-mutated tumors. The RAS-mutation status is not predictive for VEGF-inhibitors. Recent developments in the molecular characterisation of tumor cells led to the development of specific so called targeted therapies in colorectal cancer.

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Metastatic colorectal cancer

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths in the European Union and the USA [1, 2]. This malignancy involves both the large intestines (colon) and a distal portion of the colon known as the rectum. Advanced colorectal cancer refers to cancer that has spread from the colon to distant sites in the body.

For patients where resection of metastasis is not an option, palliative systemic therapy remains the treatment of choice. The aim of therapy in these patients is prolongation of survival by delaying disease progression as well as preserving physical mobility and quality of life. These objectives can be fulfilled by the usage of cytotoxic agents such as irinotecan, oxaliplatin, fluoropyrimidines, trifluridine-tipiracil [3–6] and targeted agents such as bevacizumab [7–9], aflibercept [10], ramucirumab [11], cetuximab [12, 13], panitumumab [14] and in case of Her2-expression trastuzumab [15, 16] which all have been shown to increase overall survival and time to disease progression, although some only in combination.

Treatment planning has to be individualized and takes the following aspects into consideration: overall health status, co-morbidities, co-medication, patient's attitude and expectation toward therapy, patient preferences, psychosocial factors, outcome of prior resection and adjuvant

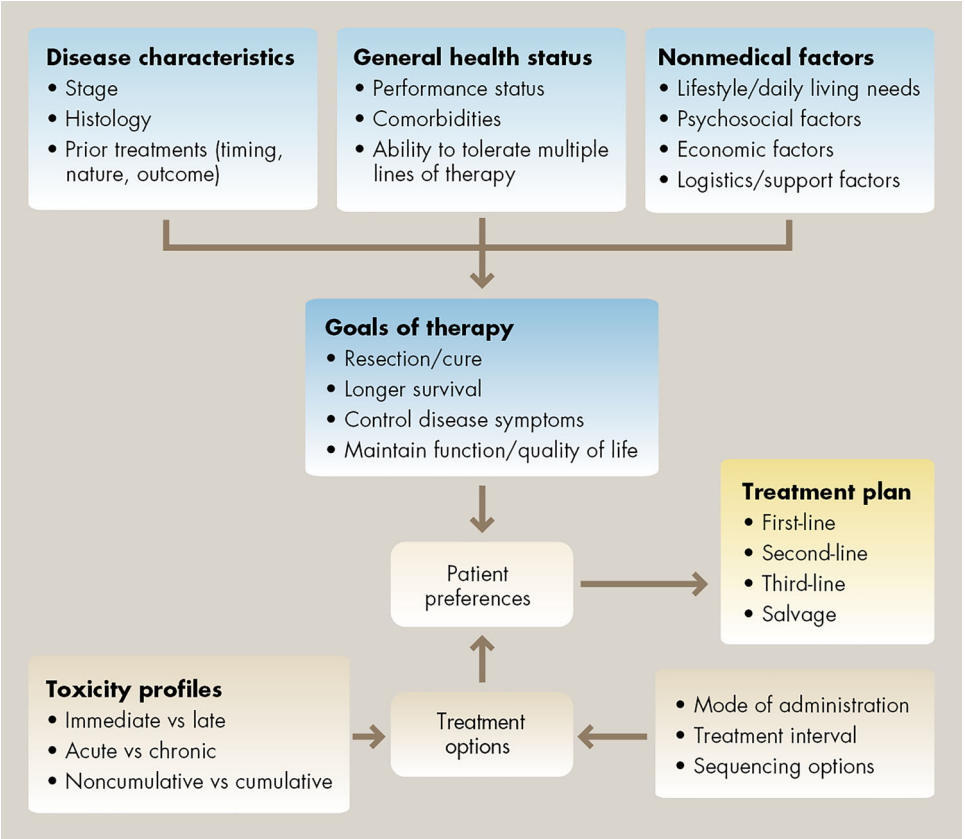

Fig. 1 Parameters of influence for treatment decision in mCRC

therapy (chemotherapy, radiation), effect on tolerability and effectiveness, overall goal of therapy, mode of administration, logistical support, consideration of side effect profiles of chemotherapy agents (Fig. 1), but also by the tumor biology (aggressive/indolent), sidedness of the primary tumor location (left vs right) [17, 18], RAS and BRAF mutational status or microsatellite instability.

The approved chemotherapeutic drugs in the EU are oxaliplatin, irinotecan, 5-fluorouracil (5-FU), capecitabine and trifluridine-tipiracil. Irinotecan- and oxaliplatin-based chemotherapies seem to have similar efficacy [3, 4] but different adverse effect profiles. Irinotecan is associated with alopecia and gastrointestinal toxicity, whereas the main side effect of oxaliplatin is cumulative neurotoxicity. Bevacizumab or monoclonal antibodies cetuximab or panitumumab can be used as companion-targeted therapy on the basis of large phase III trials [7–10] which are summarized in the current ESMO guidelines (Fig. 2).

Anti-VEGF Therapy

Several large randomized phase III trials have evaluated the role of bevacizumab in combination with chemotherapy. AVF2107 g was the first phase III trial [19] to demonstrate a survival benefit (20.3 vs 15.6 months; hazard ratio [HR], 0.66;) of bevacizumab in combination with chemotherapy in the first-line setting. The NO16966 trial [9] evaluated the efficacy of addition of bevacizumab to oxaliplatin-containing regimens, including infusional plus bolus FU, leucovorin and oxaliplatin (FOLFOX) and capecitabine and oxaliplatin (XELOX). Addition of bevacizumab modestly improved PFS (9.4 vs 8 months; HR, 0.83; $p = 0.0023$), the primary endpoint, but no significant difference in overall survival (OS; 21.3 vs 19.9 months) or response rate (RR; 47% vs 49%) was observed. One explanation for these results is that only 29% of patients in the bevacizumab arm received treatment until disease progression, compared with 47% of patients in the chemotherapy arm. Subsequent trials demonstrated that prolonged duration of bevacizumab exposure is associated with improved outcome, even if bevacizumab is continued beyond first-line progression [20].

The AVEX (Avastin in Elderly With Xeloda [21]) and TRIBE (Triplet Plus Bevacizumab [22]) trials demonstrated the safety and efficacy of bevacizumab in addition to single-agent fluoropyrimidine and chemotherapy triplet, respectively. These trials have established the role of addition of bevacizumab to chemotherapy in first-line treatment of metastatic colorectal cancer. Retrospective analysis of the randomized trials demonstrated that the benefit of bevacizumab was observed irrespective of KRAS

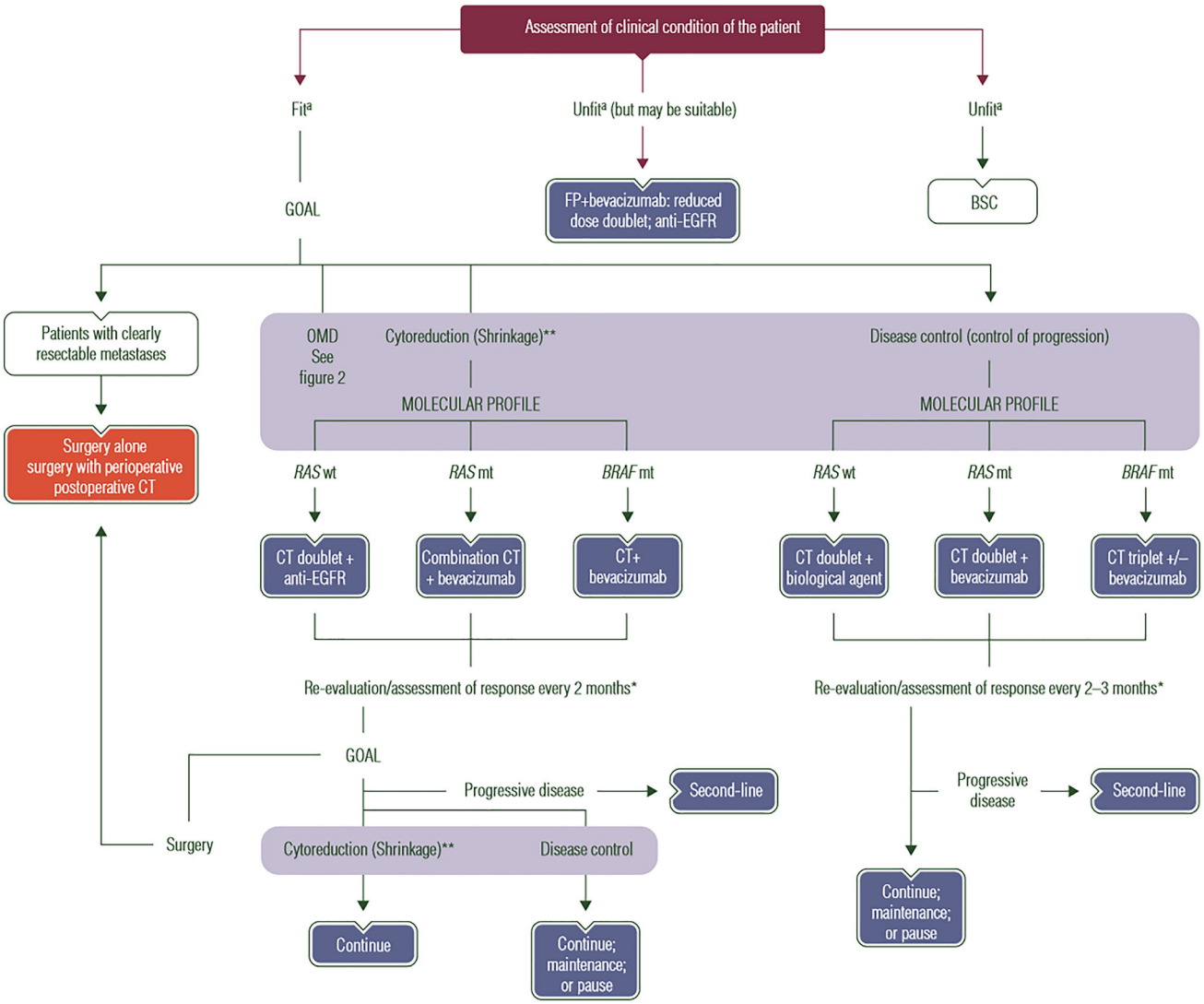

Fig. 2 ESMO treatment algorithm mCRC [54]

mutational status. The backbone cytotoxic chemotherapy seems independent in terms of efficacy with addition of bevacizumab. In terms of toxicity, bevacizumab-containing regimens are associated with hypertension, thromboembolic events, bleeding, proteinuria and GI perforation, although the likelihood of serious events (e.g., perforation) is low.

Anti-EGFR Therapy

Cetuximab and panitumumab are the two EGFR monoclonal antibodies currently approved for the treatment of metastatic colorectal cancer. Initial randomized trials included an unselected population by RAS mutation status and demonstrated only modest benefits of EGFR monoclonal antibody-containing regimens. However, retrospective analysis of these trials demonstrated that KRAS mutations conferred inherited resistance to anti-EGFR agents and that benefit was restricted to wild-type KRAS tumors [13, 14]. Predictive mutations were first noted in exon 2 (codons 12 and 13) and are present in approximately 40% of patients with metastatic colorectal cancer. Subsequent studies demonstrated that mutations in KRAS exons 3 (codons 59 and 61) and 4 (codons 117 and 146) as well as respective mutations in NRAS found in an additional 10–15% of tumors predicted similar lack of response to anti-EGFR therapies [23, 24]. In the CRYSTAL trial, 1198 unselected patients were randomly assigned to infusional plus bolus FU, leucovorin and irinotecan (FOLFIRI) with or without cetuximab. Significant improvements in RR (57% vs 40%), PFS (9.9 vs 8.4 months) and OS (23.5 vs 20 months; HR, 0.80) were documented when patients with KRAS exon 2 mutations

were retrospectively excluded [13]. Similar results were observed in the randomized phase III PRIME trial that evaluated the effect of addition of panitumumab to FOLFOX chemotherapy [14]. In both studies, the margin of improvement associated with addition of EGFR monoclonal antibodies to chemotherapy increased when all patients with KRAS and NRAS mutations were excluded [25, 26]. The results of the PRIME and CRYSTAL trials led to FDA approval of cetuximab and panitumumab for first-line treatment of metastatic colorectal cancer. Characteristic side effects of these agents are diarrhea, rash, acneiform dermatitis, stomatitis, and infusion-related reactions. Pre-emptive therapy uses skin moisturizers, sunscreens, topical steroids, and doxycycline, which can reduce incidence and severity of dermatologic toxicities associated with EGFR monoclonal antibodies [27].

Role of Primary Tumor Location and Choice of Biological Agent in the First-Line Therapy

Location of the primary tumor may have prognostic and predictive implication. Right-sided and left-sided colorectal cancers differ with respect to genetic alterations, clinicopathologic features and demographic distribution. Left-sided tumors have been shown to be associated with better prognosis in large retrospective cohorts [28]. In the FIRE-3 trial, patients with left-sided tumors had longer OS than those with right-sided tumors in both cetuximab- (38.7 vs 16.1 months) and bevacizumab-treated (28 vs 22.7 months) cohorts, but the sidedness effect was much more pronounced in the cetuximab cohort [29]. Similar results were reported in CALGB/SWOG 80405, where cetuximab was associated with decreased survival compared with bevacizumab in patients with right-sided tumors (16.4 vs 24.5 months) [30]. These results suggest that EGFR monoclonal antibodies can preferentially be considered for patients with left-sided colorectal cancers but might not be appropriate for patients with right-sided cancers.

Capecitabine

A meta-analysis indicated that capecitabine has similar OS, PFS and RR to that of infusional 5-FU [5]. The favorable toxicity profile of capecitabine and the avoidance of catheter-related complications make the oral fluoropyrimidine preferable to infusional FU. Similar considerations can be made for capecitabine plus oxaliplatin (CAPOX), where infusional FU is substituted with capecitabine in first-line treatment. Both a randomized phase III study [31] and another meta-analysis [32] in fact showed that capecitabine may safely replace 5FU in combination with oxaliplatin in first-line treatment.

Single-Agent Therapy Plus Bevacizumab

Combination of single-agent chemotherapy with a fluoropyrimidine and bevacizumab is a reasonable option in elderly patients with mCRC who cannot tolerate a cytotoxic doublet due to reduced performance status. With the combination of capecitabine plus bevacizumab, disease control can be achieved in a major proportion of the patients without the occurrence of severe side effects [21].

Triplet Therapy

A more intense chemotherapy regime uses a triplet combination of oxaliplatin, irinotecan and 5-FU (FOLFOXIRI) by which higher response rates are achieved [33]. FOLFOXIRI is mainly considered in patients with BRAFV600E mutations which carry a worse prognosis. Bevacizumab has been positively tested within a phase III trial in addition to FOLFOXIRI [22]. Triplet chemotherapy and an additional monoclonal antibody against VEGF or EGFR leads not only to improved response rates, but also shows a higher proportion of patients with early tumor shrinkage (ETS) at week 6 or 8 and a higher proportion of deepness of response (maximal tumor shrinkage). This is of utmost importance in borderline-resectable metastatic disease or highly symptomatic patients due to a high tumor load.

Trifluridine–Tipiracil

In 2014, a new chemotherapeutic agent, trifluridine–tipiracil, has been introduced in the treatment of metastatic colorectal cancer. While trifluridine–tipiracil was first approved in Japan, followed by the FDA approval in the USA in 2015, it was approved by EMA in Europe in 2016. Trifluridine–tipiracil is an oral drug consisting of tipiracil hydrochloride (TPI), which improves the bioavailability of FTD by blocking its catabolism, while trifluridine (FTD) is a reversible inhibitor that binds to the active site of thymidylate synthase (TS). The primary mode of action is DNA incorporation of FTD, which induces DNA dysfunction, including DNA strand breaks. Trifluridine–tipiracil has demonstrated a significant OS benefit in refractory mCRC in the prospective randomized clinical phase III trial RECOURSE when compared to best supportive care alone [6]. Notably, mCRC patients were all resistant to standard chemotherapies including oxaliplatin, irinotecan,

fluoropyramidine, bevacizumab, and in case of KRAS wild-type anti-EGFR antibodies. Furthermore, trifluridine–tipiracil led to a statistical significant risk reduction in progression by 52% (HR: 0.48, 95% CI, 0.41–0.57; $p < 0.001$). The oral drug is characterized by a good tolerability profile, with most likely side effects by hematotoxicity.

Regorafenib

Regorafenib is an oral small-molecule multiple kinase inhibitor with effects against several angiogenic receptor tyrosine kinases (RTKs; VEGFR-1, VEGFR-2, VEGFR-3, TIE-2), oncogenic RTKs (c-KIT, RET), stromal RTKs (PDGFR-B, FGFR-1) and intracellular signaling kinases (c-RAF/RAF-1, BRAF, $BRAF^{V600E}$). It is indicated worldwide for patients who have been previously treated with, or are not considered candidates for available therapies, including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and, if RAS wild-type, an anti-EGFR therapy. The addition of regorafenib to best supportive care prolonged median overall survival (OS; by up to 2.5 months) and progression-free survival (PFS; by up to 1.5 months) relative to the addition of placebo in the double-blind phase III studies CORRECT [34] and CONCUR [35] in patients with mCRC who had progressed after failure of standard therapy. Regorafenib-related AEs, mainly palmar–plantar erythrodysesthesia syndrome (PPES), fatigue and hypertension (HTN), were most frequent with the initial one to two cycles with gradually tapering in incidence and severity in later cycles. It is highly recommended to closely monitor for any regorafenib-related AEs, especially during the initial one to two cycles of regorafenib treatment, and to perform dose modifications as necessary.

A randomized phase II study of regorafenib dose escalation (ReDOS [36]; Arm A: 80 mg/day, weekly dose escalation if no significant drug-related toxicities, up to 160 mg/day) versus standard dose (Arm B: 160 mg/day) investigated tolerability and efficacy. Considering the proportion of patients who completed two cycles of treatment and initiated the third showed that weekly dose escalation of regorafenib from 80 to 160 mg/day was superior to a starting dose of 160 mg/day. OS was superior with weekly dose escalation compared to standard dosing (9.0 months vs 5.9 months, HR 0.65).

Oligometastatic Disease

Oligometastatic disease is characterized by the localization of the disease to a few sites and lesions and is associated with the option to use local ablative therapy approaches in order to improve disease control and clinical outcome. Treatment strategies for patients with oligometastatic disease should be based on the possibility of achieving complete resolution of all tumor masses, using surgical R0 resection (complete resection with clear resection margins and no evidence of microscopic residual tumor) and/or localized interventions, either initially or possibly after induction treatment with systemic therapy.

Options for localized therapy include stereotactic ablative body radiotherapy (SBRT [37]) and radiofrequency ablation (RFA [38]) for visceral or nodal involvement, peritonectomy with or without hyperthermic intraperitoneal chemotherapy (HIPEC [39]) for peritoneal disease, and nodal dissection. The management of this subgroup of patients is becoming increasingly complex, and it is imperative to take any treatment decision within a multidisciplinary tumor board.

Therapy of Molecular Subgroups: BRAF Mutations

BRAFV600E mutation is the most common BRAF mutation in mCRC accounting for almost 99% of all mutations. BRAFV600E mutations account for 8–12% of mCRC and are associated with female sex, advanced age, right-sided tumor location in the colon and high-grade histology [40]. In most studies, median overall survival in patients with BRAF-mutant mCRC is around 1 year compared with 2–3 years in patients with BRAF wild-type tumors [41].

BRAF-mutated mCRC is resistant to single-agent BRAF inhibition [42] with an overall response rate of around 5%. In order to induce more durable responses to BRAF inhibitor therapy, recent investigative approaches have focused on novel-targeted therapy combinations. Dual inhibition of BRAF and EGFR has been shown to produce sustained suppression of signaling pathways to overcome EGFR-driven resistance in vitro and in xenograft models of CRC [43].

A phase II, randomised, open-label trial evaluated the BRAF kinase inhibitor vemurafenib in combination with irinotecan and cetuximab (VIC) compared with irinotecan plus cetuximab (IC) in 106 patients with BRAF V600E-mutated mCRC previously treated with one or two standard chemotherapy regimens [44]. OS was not reported, but VIC resulted in longer median PFS versus IC. An excess of grade 3–4 nausea, neutropaenia and anemia was reported

for VIC compared with IC. Based on the results of this trial, the combination of vemurafenib, irinotecan and cetuximab is an emerging standard-of-care option in the second-line setting.

Because MEK plays a critical role in EGFR-driven resistance to BRAF inhibition, recent studies have investigated combinations of BRAF, EGFR and MEK inhibitors [45]. A phase 1/2 study [46] evaluated the activity of dabrafenib, panitumumab and trametinib in patients with BRAF-mutated mCRC. Patients received doublet dabrafenib plus panitumumab or doublet trametinib plus panitumumab or triplet dabrafenib, panitumumab and trametinib. The response rate with dabrafenib plus panitumumab was 10% compared to 21% with the triplet. The addition of dabrafenib to panitumumab and trametinib appeared to reduce skin-related toxicities.

Currently a phase III trial is under way to assess the activity and safety of encorafenib (BRAF inhibitor) plus cetuximab (EGFR inhibitor) with or without bimetinib (MEK inhibitor) versus cetuximab plus chemotherapy in patients with previously treated BRAF V600E-mutant mCRC (BEACON trial [47]).

Therapy of Molecular Subgroups: Her2 Mutations

More experimental approaches were focusing on rare molecular aberrations: In this context, Her2 overexpressing mCRC was targeted by dual inhibition using trastuzumab plus lapatinib. In the HERACLES trial [15] in approximately 80% of patients, a disease control could be achieved in heavily pretreated setting. A second trial showed similar efficacy when trastuzumab was used in combination with pertuzumab in heavily pretreated patients [16].

Immunotherapy in mCRC

Immunotherapy has proven effectiveness in the subgroup of pretreated mismatch-repair-deficient/microsatellite instable (MSI) colorectal cancer in stage IV. The proportion of MSI patients with metastatic colorectal cancer is estimated to be 3–4% [48]. First evidence was provided by Le et al. [49] in a small number of patients, who were suffering from hereditary non-polyposis colon carcinoma (HNPCC), thus bearing a mismatch-repair deficiency. In this particular study, 89% of colorectal cancer patients had a disease control with 57% partial response when treated with pembrolizumab monotherapy, while the mismatch-repair proficient tumors had no benefit from this treatment.

Furthermore, data from the Checkmate-142 trial were presented [50], which considered also mismatch-repair-deficient/MSI-high metastatic colorectal cancer patients, but was not limited to hereditary pathogenesis of the disease. In one cohort of pretreated mCRC patients, nivolumab 3 mg/kg was used as a monotherapy, which resulted in 31% response rate and 69% disease control $\geq$ 12 weeks. The median progression-free survival (PFS) was 9.6 months, whereby 45.6% of the patients were still free of progression at 12 months according to a centrally blinded assessment. The 12-month overall survival was 73.8%, notable in pretreated mCRC patients. A second cohort (n = 84) of the checkmate 142 study assessed the efficacy of a combination strategy by using nivolumab plus ipilimumab (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3 W for four cycles followed by nivolumab 3 mg/kg monotherapy q = 14d). As expected, both, the efficacy and the toxicity were higher. However, after 12 weeks in 79% of the pretreated mCRC patients a disease control was recorded (ORR 55%). Notably, the accompanied biomarker analysis revealed that PD-L1 expression was agnostic. Furthermore, also the RAS-, BRAF-, as well as the pathogenesis for the mismatch-repair deficiency (hereditary/acquired) was not predictive for the treatment response.

This concept also active in first-line was recently presented by Heinz-Josef Lenz and co-workers at the ESMO 2018 meeting [51]. The authors could demonstrate that the combination of ipilimumab plus nivolumab led in 84% of patients to a reduction from baseline of tumor burden. 77% of the patients were still progression-free at 12 months, and the median PFS was not reached. Notably, 83% of the patients were alive after 12 months when treated with these anti-CTLA-4 plus anti-PD-1 inhibitors.

While immunotherapy in MMR-d/MSI-high metastatic carcinomas has been approved in the USA by the FDA, an approval is still pending in the European Union by the EMA.

Recent data suggest that neoadjuvant ipilimumab plus nivolumab treatment might also be beneficial in MSI-h/MMR-d patients as first results from the NICHE study have been demonstrated at ESMO 2018 [52].

While the MMR-d/MSI-h status seems to be a strong positive predictor of response for immunotherapy, the activity in the MMR-proficient/MSI-stable tumors seems to be limited. Experimental combinations, such as atezolizumab plus cobimetinib, have been assessed in the IMblaze370 trial (NCT02788279). In this clinical phase III trial, patients with microsatellite-stable CRC atezolizumab plus cobimetinib have been compared with regorafenib and atezolizumab monotherapy. The mCRC patients have received before at least two lines of therapy. The results, however, did not demonstrate a superior effect of atezolizumab plus cobimetinib combination when compared to Regorafenib [53].

In summary, while immunotherapy has been demonstrated to be very active in MMR-d/MSI-h mCRC patients, there is an urged need to define strategies to convert immunologic "cold" microsatellite-stable tumors into "hot" tumors.

Molecular characterization of the individual tumor is already leading to a better treatment stratification and mCRC might become similar to lung cancer another example for an more individualized treatment approach. However, there is need to identify all drivers to consequently adapt our treatment.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

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