VIA MEDICA

REVIEW ARTICLE

Piotr J. Wysocki

Department and Clinic of Oncology, Jagiellonian University Medical College, Cracow, Poland

Recent progress in the systemic treatment of colorectal cancer

Address for correspondence:
Prof. dr hab. n. med. Piotr Wysocki
Department and Clinic of Oncology,
Jagiellonian University Medical College,
Cracow, Poland
e-mail: piotr.wysocki@uj.edu.pl

Oncology in Clinical Practice
2021, Vol. 17, No. 4, 157–163
Translation: dr n. med. Dariusz Stencel
DOI: 10.5603/OCP.2020.0044

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Over the last decade in the treatment of colorectal cancer (CRC) patients, a significant improvement of systemic treatment approaches has been observed in terms of safety and efficacy. Regarding safety, a huge, international IDEA trial proved that for CRC patients with pT1–3 and N1 features, a short, 3-month adjuvant treatment with CAPOX does not negatively impact long-term prognosis compared to standard, 6-month, oxaliplatin-based regimens. Additionally, the shortened adjuvant treatment significantly diminishes chronic neuropathy risk, representing a detrimental symptom in CRC survivors. On the other hand, in a palliative setting, a significant improvement in mCRC patients' prognosis has been achieved with the advent of novel therapies targeting critical molecular disorders. The encorafenib and cetuximab combination in *BRAF V600E* mutated mCRC and checkpoint inhibitors in MSI-H mCRC patients are the most impressive examples of this continuous progress.

Key words: colorectal cancer, metastases, cetuximab, encorafenib, pembrolizumab, immunotherapy, microsatellite instability, *BRAF* mutation, adjuvant treatment

Oncol Clin Pract 2021; 17, 4: 157–163

Introduction

Colorectal cancer (CRC) is diagnosed in approximately 1.4 million individuals around the world every year, including over 18,000 individuals in Poland [1, 2]. Due to the unsatisfactory 5-year survival rates (< 60% in Europe, < 50% in Poland) intensive development of new, more effective diagnostic and therapeutic strategies for both, early and generalized disease stage, is necessary. Advances in improving prognosis in CRC patients has to pertain to different aspects of diagnostics, surgical and perioperative treatment at an early stage of a neoplastic process, as well as systemic and supportive therapies in patients with metastatic disease. New systemic treatment strategies based on new chemotherapeutic agents and molecularly targeted drugs have significantly improved the prognosis of patients with advanced colorectal cancer in the last 20 years. As a result, the average survival time of patients with generalized CRC increased almost four times from less than 10 months to over 30 months [3]. Despite significant progress in the diagnosis and treatment of CRC, for epidemiological reasons, the number of patients is increasing every year, both those after treatment failure, and those in whom palliative systemic treatment has exhausted its activity or was no longer active. Therefore, improving the prognosis in CRC patients must include both improvements of the effectiveness and safety of palliative and radical treatment. This review summarizes the most important recent changes in the systemic treatment of patients with colorectal cancer.

Adjuvant therapy

Adjuvant chemotherapy – based on 5-fluorouracil (5-Fu) – allowed for a significant improvement in the prognosis of patients with stage III CRC. A meta-analysis of seven clinical trials of adjuvant chemotherapy with 5-Fu showed a significant reduction in the risk of death by 13–15 percentage points [4]. The 5-year overall survival rates were 58% and 71% in patients with

1–4 lymph nodes involved, and 29% and 44% in the case of 5 or more lymph nodes involved for placebo and 5-Fu, respectively. The next step on the way to optimizing the adjuvant treatment was to identify the most safe form of 5-fluorouracil administration, which proved to be a two-day infusion. Similarly, capecitabine has been shown to be as effective as 5-Fu but less toxic compared to 5-Fu administered by injections [5]. Another progress in improving the effectiveness of adjuvant therapy was related to the introduction of two-drug regimens based on 5Fu and oxaliplatin combination [6, 7]. In the MOSAIC study, the use of the FOLFOX regimen in patients with stage III colorectal cancer significantly increased the 5-year disease-free survival rate from 59% to 66% and 6-year overall survival rate from 69% to 73% as compared to 5Fu + Lv [6]. As with 5-Fu alone, the two-drug regimen did not provide any benefit for stage II CRC. However, the improved prognosis associated with the use of oxaliplatin resulted in significant neurotoxicity, which persisted in 24% of patients beyond 18 months after the completion of adjuvant therapy and significantly influenced the quality of life. Similarly to FOLFOX, the CAPOX regimen was also more active than 5-FU monotherapy, significantly increasing the 7-year DFS rate from 56% to 63% and 7-year OS rate from 67% to 73%, with similarly increased neurological toxicity [7]. The recent progress in the adjuvant treatment of CRC is not leading to further improvement of the prognosis but is related to the increased safety of postoperative chemotherapy.

The International Duration Evaluation of Adjuvant Therapy (IDEA) study was aimed to assess the possibility of shortening the duration of adjuvant treatment by half (from 6 to 3 months). Data from six parallel, prospective clinical trials (IDEA, SCOT, CALGB/SWOG80702, ACHIEVE, TOSCA, HORG) were analysed, including a total of 13,000 patients with stage III CRC who received adjuvant chemotherapy with CAPOX or FOLFOX regimens for 3 or 6 months [8]. The study was to verify whether 3-month adjuvant therapy is comparably effective (non-inferior) as 6-month treatment; however, after a follow-up of 42 months, it was not possible to confirm the non-inferiority. The 3-year disease-free survival (DFS) rates, the primary endpoint of the study, were 74.6% in the 3-month treatment group and 75.5% in the 6-month treatment group. Patients receiving shorter adjuvant therapy had significantly fewer and less severe side effects compared to standard adjuvant chemotherapy. Grade ≥ G2 neuropathy was reported in 16.6% (FOLFOX) and 14.2% of patients (CAPOX) receiving 3-month therapy, and 47.7% and 44.9% of patients receiving 6-month therapy, respectively. Although it was not possible to prove the comparability of two adjuvant treatment approaches in the overall study population, pre-planned subgroup analyses revealed several important relationships. First, a significant advantage of 6-month FOLFOX6 regimen over 3-month treatment [hazard ratio (HR) = 1.16; 95% confidence interval (CI) 1.06–1.26; p = 0.001] was demonstrated with a difference in the 3-year DFS rates of 2.4 percentage points (73.6% versus 76%). In turn, in the case of the CAPOX chemotherapy regimen, no significant differences were found between the shorter and longer duration of therapy — HR 0.95 (95% CI: 0.85–1.06). The 3-year DFS rates for CAPOX were 75.9% (3 months of treatment) and 74.8% (6 months of treatment). In patients with disease stage not exceeding pT3 and pN1, 3-month CAPOX therapy was as effective as 6-month therapy (3-year DFS rates — 85.0% versus 83.1%, respectively; HR = 0.85; 95% CI: 0.71–1.01). On the other hand, in the group of patients with stage > pT3 or > pN1, 3-month CAPOX therapy was significantly worse than 6-month therapy [8].

The updated results of the IDEA study, after a median follow-up of 72 months, were presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting [9]. In the general patients' population, the 5-year overall survival (OS) rate was 82.8% (6-month therapy) versus 81.4% (3-month therapy), demonstrating a borderline significance in terms of non-inferiority. On the other hand, in the general patients' population, the advantage of standard chemotherapy over 3-month therapy was still maintained in relation to the 5-year DFS rates. The updated results of the IDEA study clearly confirmed the possibility of using 3-month CAPOX chemotherapy in patients with advanced disease (pT1–T3 and pN1). In this subgroup, the 5-year DFS rate was 90.4% (3 months) versus 88.1% (6 months) with a hazard ratio for DFS of 0.85 (95% CI: 0.69–1.04). The comparison of toxicity of 3- and 6-month regimens showed that shorter chemotherapy was associated with reduced incidence of various adverse events (2 to 6-fold), including a 3-fold reduction in the risk of G2 or higher neurotoxicity. Thus, based on the results of the IDEA study, the option of 3-month adjuvant chemotherapy based on the CAPOX regimen should become a routine clinical practice in patients with colorectal cancer T1–3 and N1 [9].

Palliative therapy

Over the last two decades, the progress in the treatment of patients with advanced CRC has been related to the introduction of new cytotoxic drugs — irinotecan, oxaliplatin, trifluridine with tipiracil and molecularly targeted drugs — anti-EGFR antibodies (cetuximab, panitumumab), VEGF scavengers (bevacizumab, aflibercept) and the VEGFR tyrosine kinase inhibitor (regorafenib). Despite a remarkable increase in life expectancy in the general population of patients with advanced CRC after introducing the new drugs and se-

quential treatment strategies, so far the smallest benefit was observed in patients with mutations of the KRAS, NRAS and BRAF kinases regulating the key intracellular MAPK (RAS/RAF/MEK/ERK) signalling pathway. It was mainly associated with the neutralization of the anti-tumour activity of anti-EGFR antibodies used both as monotherapy and in combination with chemotherapy.

The activity of the MAPK pathway induces proliferation, differentiation, migration, survival and angiogenesis processes. Abnormal activation of the MAPK pathway is a phenomenon observed in many cancers, e.g. melanoma, lung, colorectal or pancreatic cancers, and most often results from the abnormal function of RAS and BRAF signalling kinases harbouring activating mutations [10]. *RAS* mutations occur in 9–30% of all cancers, including *KRAS* (86%), *NRAS* (11%) and *HRAS* (3%) mutations [11]. The frequency of mutations in CRC depends on the location of the neoplastic process. *NRAS* mutations occur with a similar frequency throughout the intestine (about 6.5%), and *KRAS* mutations are more common in the right part of the colon (46%) than in the left part (35.8%) [12]. On the other hand, *BRAF* activating mutations occur 4 times more often in the right than the left part of the large intestine (16.3% *vs.* 4.3%, respectively) [12].

BRAF-targeted therapy

The process of neoplastic transformation of CRC with the *BRAF V600* activating mutation does not depend on the typical phenomenon commonly observed in this tumour, i.e., inactivation of the *APC* gene. *BRAF* activating mutation, occurring in about 8% of CRC patients, is a critical mutation initiating the process of neoplastic transformation in serrated polyps in which, instead of chromosomal instability, extensive DNA methylation occurs within the CpG islands (CGIs) [13]. Methylation can lead to the extinction of the promoter function of genes responsible for DNA repair, e.g., *MLH1*, which in turn causes microsatellite instability. Accordingly, microsatellite instability (MSI-H) is observed in 60% of intestinal cancers with *BRAF* gene mutation. *BRAF* activating mutations are more common in female patients and older age [14], and their presence is associated with lower differentiation, mucous histology, and greater local tumour advancement [15]. *BRAF* activating mutation is an unfavourable prognostic factor in patients with metastatic CRC. In the FOCUS study evaluating various strategies of systemic sequential CRC treatment, the risk of death was 82% higher (HR = 1.82; 95% CI: 1.36–2.43) in patients with mutated *BRAF* gene [16]. The meta-analysis of the above-mentioned study and CAIRO, CAIRO2, and COIN studies showed not only a 91% higher relative risk of death (HR = 1.91; 95% CI: 1.66–2.15), but also a significantly higher relative risk of progression or death (HR = 1.34; 95% CI: 1.17–1.54) [17].

The first attempts to block the function of mutant BRAF kinase were based on the BRAF inhibitor vemurafenib. In a study of 21 previously treated CRC patients with *BRAF V600E* mutation, clinical benefit (including one partial response) was shown in 8 patients, with median PFS and OS of 2.1 and 7.7 months, respectively [18]. In general, the obtained results were much less spectacular compared to the parallel studies in patients with advanced melanoma, but they indicated some activity of the strategy based on blocking of mutant BRAF kinase in CRC patients. Translational research identifying the mechanisms of resistance to treatment with a BRAF inhibitor in CRC patients with the *BRAF V600E* mutation showed that blocking the MAPK pathway triggers a feedback loop activating the membrane EGFR receptor and the parallel signalling pathway PI3K/AKT/mTOR cross activating the MAPK pathway downstream of BRAF kinase [19]. These findings resulted in attempts to combine vemurafenib and cetuximab. In the group of 27 CRC patients with *BRAF V600* mutation, after the failure of prior treatment (median 2 lines, range 1–6), half of the patients showed tumour shrinkage, meeting the criteria for partial response in 1 patient. Median PFS and OS were 3.7 and 7.1 months, respectively [20]. In turn, the combination of panitumumab with vemurafenib in a population of 15 CRC patients with *BRAF V600* allowed the disease control (at least stabilization) in 10 patients [21]. The combination of panitumumab with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) was evaluated in 24 patients with colorectal cancer with the *BRAF V600E* mutation, in whom this triple therapy resulted in a 21% objective response rate, with median PFS and OS of 4,1 months and 9.1 months, respectively [22]. Another BRAF inhibitor, encorafenib, in combination with cetuximab produced a 23% objective response rate and 54% disease stabilization rate, with a median PFS of 3.7 months [23]. The next step in the development of targeted therapies in the treatment of patients with a *BRAF* activating mutation were the attempts to combine targeted drugs with chemotherapy. In 2012, preclinical data appeared indicating the high effectiveness of vemurafenib, cetuximab and irinotecan combination [24]. A phase I study showed that the combination of these three drugs in CRC patients with *BRAF V600E* mutation-induced objective responses rate of 35% with a median PFS of 7.7 months. The same regimen was compared in a phase II study involving 106 patients with the combination of irinotecan and cetuximab. The addition of vemurafenib significantly reduced the relative risk of progression by more than half (HR = 0.42, $p < 0.001$) with a 4-fold increase in objective responses

(from 4% to 16%) and a 3-fold improvement in the disease control rate (from 22% to 67%) [25].

A ground-breaking phase III study (BEACON CRC) in patients with advanced CRC with *BRAF V600* mutation compared two experimental regimens: a triple [encorafenib (BRAF inhibitor), binimetinib (MEK inhibitor), cetuximab] and double therapy (encorafenib, cetuximab) with standard chemotherapy (irinotecan + cetuximab or FOLFIRI + cetuximab) [26]. In total 665 patients with metastatic CRC with *BRAF V600E* mutation were randomized in a 1:1:1 ratio to three arms receiving one of the above-mentioned systemic treatment strategies. The primary endpoints of the study were OS and objective response rate in the arm receiving triple therapy compared to standard chemotherapy. The median OS in the triple therapy arm was 9.0 months compared to 5.4 months in the control arm, which translated into a significant, almost 50% reduction in the relative risk of death (HR = 0.52; 95% CI: 0.39–0.70). Additionally, in the triple therapy arm, the objective response rate was 6 times higher than in the control arm (26% *vs.* 4%), the percentage of patients with clinical benefit was also higher (69% and 31%), and progression at first post-baseline assessment was found in 10% of patients receiving triple therapy and 34% of patients receiving chemotherapy. In the case of experimental double therapy, the median OS was 8.4 months, which translated into a significant reduction in the risk of death by 40% compared to the control arm (HR = 0.60; 95% CI: 0.45–0.79). The objective response rate in the experimental double therapy arm was 20%, clinical benefit was 74%, and progression at first post-baseline assessment was found only in 7% of patients. In the summary of adverse reactions in the BEACON CRC study, the best-tolerated regimen was the combination of encorafenib with cetuximab, for which fewer adverse events of G3 or higher severity (50% *vs.* 58% and 61%), diarrhoea (33% *vs.* 58% and 48%), including G3 severity (2% *vs.* 10% and 10%), and rash (29% *vs.* 49% and 39%) were reported compared to the triple regimen and chemotherapy. The analysis with use, among others, EORTC QLQ C30, FACT-C questionnaires, has shown a beneficial effect on the quality of life and the prolongation of time to QoL deterioration in patients receiving experimental regimens compared to chemotherapy [27]. In June this year, the European Medical Agency (EMA) has approved encorafenib in combination with cetuximab for the treatment of patients with metastatic CRC with *BRAF V600E* mutation after the failure of prior chemotherapy.

Microsatellite instability

Microsatellite instability (MSI-H) is a molecular disorder typical for Lynch syndrome that was first described in hereditary nonpolyposis colon cancer (HNPCC), accounting for 0.2–6% of this cancer. This is associated with impairment of the functions of the *MSH2*, *MLH1*, *PMS1* and *PMS2* genes belonging to the group of DNA mismatch repair (MMR) genes encoding the MMR proteins responsible for the repair of mismatched bases. The alterations in these genes lead to impaired DNA repair, resulting in microsatellite instability. Deficient MMR (dMMR) mechanisms prevent the correction of spontaneous errors that occur during DNA replication (e.g., base replacement, insertion or deletion of short fragments of DNA strands). About 15% of sporadic colorectal cancers show microsatellite instability, including 3% of cancers developing in carriers of hereditary mutations of DNA repair genes (Lynch syndrome), and the remaining 12% related to methylation of the *MLH1* gene promoter [28]. Methylation of the *MLH1* promoter region, as already mentioned, is strongly associated with *BRAF V600* mutation [29]. Colorectal cancers with MSI-H have some typical features — right-sided location, low differentiation, extracellular mucus secretion, and rich lymphocytic infiltrates [28, 30]. At the stage of metastatic disease, MSI-H colorectal cancers are characterized by a higher incidence in older patients, especially women, and synchronous metastases more often in the peritoneum or lymph nodes than in the liver [31]. Deficient MMR mechanisms lead to the accumulation of mutations in the cell and the formation of the so-called hypermutator profile. In cancer cells with dMMR, abnormal proteins formed on the matrix of damaged genes can be recognized by the immune system as foreign (antigens), which in turn leads to an increase in cell immunogenicity. As the condition for the progression of a neoplastic disease characterized by high immunogenicity is the impairment of the immune mechanisms of the specific antitumor response, tumours with microsatellite instability often express suppressor molecules such as PD-L1, PD-L2 [32]. In connection with this in the case of neoplasms with microsatellite instability, the effectiveness of immunotherapy began to be intensively assessed.

One of the first studies on checkpoint inhibitors in the treatment of patients with MSI-H CRC was the phase II MK-3475 trial with pembrolizumab. This study included 41 patients with chemoresistant solid tumours, including 32 patients with CRC (11 MSI-H and 21 without microsatellite instability - MSI-L), with > 70% patients receiving more than 3 lines of prior systemic treatment [33]. The objective response rate and disease control rate were 40% and 90%, respectively, in MSI-H CRC patients versus 0% and 11% in the MSI-L population. The use of pembrolizumab in patients with CRC MSI-H was associated with a significant reduction in the relative risk of progression and death by 90% (HR = 0.10, $p < 0.001$) and death alone by 80% (HR = 0.20, $p < 0.05$) with a median of PFS and OS in CRC MSI-L patients of

2.2 and 5.0 months, respectively. Recent publications of the MK-3475 study after 12 months of follow-up indicate that the median of PFS and OS in MSI-H patients has not yet been achieved [34].

Phase III Keynote-177 study enrolled 307 previously untreated patients with advanced MSI-H/dMMR CRC. Patients were randomized in a 1:1 ratio to either the experimental arm receiving pembrolizumab monotherapy (200 mg every 3 months for up to 35 courses) or the control arm receiving chemotherapy (mFOLFOX6 or FOLFIRI used alone or in combination with biological drug bevacizumab or cetuximab). After a median follow-up of 32.4 months, it was shown that pembrolizumab was associated with a significant reduction in the relative risk of progression by 40% (HR for PFS = 0.60; 95% CI: 0.45–0.80) with more than two-fold difference in the medians PFS (16.5 *vs.* 8.2 months) and 2-year PFS rates (48% and 19%) in the experimental and control arm, respectively [35]. In the pembrolizumab arm, there was a higher objective response rate, (43.8% *vs.* 33.1%), including a complete response rate (11.1% *vs.* 3.9%). At the same time, however, a greater percentage of patients did not respond to the treatment in the pembrolizumab arm (disease progression at the first post-baseline assessment was 29.4% for immunotherapy versus 12.3% for chemotherapy). PFS subgroup analyses showed that only patients with *KRAS* or *NRAS* genes mutations did not benefit from immunotherapy. Adverse reactions in CTC grade 3–5 were almost three times more frequent in the pembrolizumab arm (66%) than in the chemotherapy arm (22%).

Another checkpoint inhibitor evaluated in patients with MSI-H CRC was nivolumab. In the phase II CheckMate142 study, the combination of nivolumab and low-dose ipilimumab was assessed in the population of patients with metastatic MSI-H/dMMR CRC. In a group of 45 patients, nivolumab was administered every 2 weeks and ipilimumab every 6 weeks. The objective response rate was 69%, including a complete response rate of 13%, and the disease control rate of 84% [36]. The median duration of response, PFS or OS was not reached, and the 24-month PFS and OS rates were 74% and 79%, respectively. Disease progression at the first post-baseline assessment was observed in 13% of patients. Combined double immunotherapy was associated with the occurrence of CTC G3-4 side effects in 22% of patients, and discontinuation of treatment, for this reason, was necessary for 7%.

KRAS-targeted therapy

The *KRAS* gene is the most commonly mutated oncogene in human tumours. It encodes KRAS GTPase, which is an element of signal transduction within the MAPK cascade (RAS-RAF-MEK-ERK), which also has the potential to activate the PI3K-AKT-mTOR pathway. For this reason, *KRAS* mutations have a key impact on inducing an aggressive phenotype of cancer cells, inducing their proliferation, stimulating survival, production of key proteins and resistance to pro-apoptotic signals. The *KRAS* gene mutation, similarly to *NRAS* or *BRAF*, is a negative predictor of the response to anti-EGFR antibodies because it makes intracellular signalling independent of the function of the EGFR transmembrane receptor. For a very long time, it seemed that KRAS was a protein for which targeted pharmacological blockade would not be possible at all. The *KRAS* p.G12C mutation (replacement of glycine with cysteine at position 12) occurs in approximately 13% of non-small cell lung cancers and 1–3% of colon cancers and other solid tumours. In a phase I study, sotorasib — an irreversible, small molecule $KRAS^{G12C}$ inhibitor was evaluated in a population of 130 patients with advanced solid tumours with *KRAS* p.G12C mutation (including 42 CRC patients), most of whom received at least 3 lines of prior systemic treatment [37]. In CRC patients with the *KRAS* p.G12C mutation, sotorasib enabled disease control in 74% of patients (including 7% of partial responses), and disease progression was observed in 24% of patients. Serious adverse events (SAEs) of sotorasib were observed in 45% of patients in the overall population, including 7% of SAEs leading to treatment discontinuation. The most common adverse events (≥ G3) were diarrhoea, weakness, nausea and vomiting, abdominal pain, and dyspnoea and cough. Sotorasib is the first active KRAS inhibitor demonstrating the activity in patients with solid tumours with the *KRAS* p.G12C mutation; however, its activity in colorectal cancer seems to be markedly lower than in non-small cell lung cancer.

Summary

The progress that has been made in recent years in the field of treatment of patients with CRC relates not only to the improvement of effective palliative treatment but also the effective and safe pharmacological treatment with curative intent. The results of the IDEA study indicate the possibility of de-escalating adjuvant treatment and minimizing the risk of chronic side effects in a group of relatively low-stage patients who require double chemotherapy. It seems that the CAPOX regimen should be the first-line treatment in all patients with stage III CRC. In patients with T1–3 and N1 tumours, it allows to use only a 3-month adjuvant therapy, and in all patients, regardless of the initial stage, it allows to reduce the frequency of visits and prevent hospitalization, which, especially in the current epidemic situation, is of key importance for patient safety.

Regarding palliative treatment, the emergence of new targeted therapies dedicated to more and more sophisticated patient populations is observed. Contrary to the routinely available targeted therapies where anti-angiogenic treatment (bevacizumab, aflibercept, regorafenib or ramucirumab) is indicated for all patients with advanced CRC with no contraindications, and anti-EGFR antibodies are indicated in almost half of the patients, the use of new therapies will be much more limited. Immune checkpoint inhibitors are potentially intended for approximately 12% of MSI-H CRC patients, BRAF inhibitors for 8% of patients with the *BRAF V600E* mutation, and the KRAS inhibitor sotorasib for 1–3% of patients with the *KRAS* p.G12C mutation. There is no doubt, however, that better and better personalization and optimization of systemic treatment is the right direction to improve the possibilities of active and safe systemic treatment of patients with advanced colorectal cancer.

Unfortunately, in Poland, the biggest problem in improving the prognosis of patients with advanced CRC is still the reimbursement limitations in access to new, active therapies such as BRAF inhibitors or anti-PD1 antibodies. In this context, however, one should remember the possibilities offered by the procedure of individual financing of therapy as part of emergency access to drug therapies. These limitations, however, do not pose any problems in the case of adjuvant treatment, where incorporation of the IDEA study results into clinical practice is possible without delay.

Conflict of interest

Speaker, advisory honoraria from Roche, Merck, Amen, Servier. Travel grants — Merck, Roche.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359–E386, doi: 10.1002/ijc.29210, indexed in Pubmed: 25220842.
2. Didkowska J. Zachorowania i zgony na nowotwory złośliwe w Polsce. Krajowy Rejestr Nowotworów, Centrum Onkologii - Instytut im. Marii Skłodowskiej - Curie. 2019.
3. Jawed I, Wilkerson J, Prasad V, et al. Colorectal cancer survival gains and novel treatment regimens: a systematic review and analysis. JAMA Oncol. 2015; 1(6): 787–795, doi: 10.1001/jamaoncol.2015.1790, indexed in Pubmed: 26181239.
4. Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2009; 27(6): 872–877, doi: 10.1200/JCO.2008.19.5362, indexed in Pubmed: 19124803.
5. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005; 352(26): 2696–2704, doi: 10.1056/NEJMoa043116, indexed in Pubmed: 15987918.
6. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009; 27(19): 3109–3116, doi: 10.1200/JCO.2008.20.6771, indexed in Pubmed: 19451431.
7. Schmoll HJ, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011; 29(11): 1465–1471, doi: 10.1200/JCO.2010.33.6297, indexed in Pubmed: 21383294.
8. Grothey A, Sobrero AF, Shields AF, et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. N Engl J Med. 2018; 378(13): 1177–1188, doi: 10.1056/NEJMoa1713709, indexed in Pubmed: 29590544.
9. Sobrero A, Andre T, Meyerhardt J, et al. Overall survival (OS) and long-term disease-free survival (DFS) of three versus six months of adjuvant (adj) oxaliplatin and fluoropyrimidine-based therapy for patients (pts) with stage III colon cancer (CC): Final results from the IDEA (International Duration Evaluation of Adj chemotherapy) collaboration. J Clin Oncol. 2020; 38(15_suppl): 4004, doi: 10.1200/jco.2020.38.15_suppl.4004.
10. Pritchett TR, Lieskovsky G, Skinner DG. Extension of renal cell carcinoma into the vena cava: clinical review and surgical approach. J Urol. 1986; 135(3): 460–464, doi: 10.1016/s0022-5347(17)45691-6, indexed in Pubmed: 3944886.
11. Cox AD, Fesik SW, Kimmelman AC, et al. Drugging the undruggable RAS: Mission possible? Nat Rev Drug Discov. 2014; 13(11): 828–851, doi: 10.1038/nrd4389, indexed in Pubmed: 25323927.
12. Bylsma LC, Gillezeau C, Garawin TA, et al. Prevalence of RAS and BRAF mutations in metastatic colorectal cancer patients by tumor sidedness: A systematic review and meta-analysis. Cancer Med. 2020; 9(3): 1044–1057, doi: 10.1002/cam4.2747, indexed in Pubmed: 31856410.
13. Sanz-Garcia E, Argiles G, Elez E, et al. BRAF mutant colorectal cancer: prognosis, treatment, and new perspectives. Ann Oncol. 2017; 28(11): 2648–2657, doi: 10.1093/annonc/mdx401, indexed in Pubmed: 29045527.
14. Gonsalves WI, Mahoney MR, Sargent DJ, et al. Alliance for Clinical Trials in Oncology. Patient and tumor characteristics and BRAF and KRAS mutations in colon cancer, NCCTG/Alliance N0147. J Natl Cancer Inst. 2014; 106(7), doi: 10.1093/jnci/dju106, indexed in Pubmed: 24925349.
15. Clancy C, Burke JP, Kalady MF, et al. BRAF mutation is associated with distinct clinicopathological characteristics in colorectal cancer: a systematic review and meta-analysis. Colorectal Dis. 2013; 15(12): e711–e718, doi: 10.1111/codi.12427, indexed in Pubmed: 24112392.
16. Richman SD, Seymour MT, Chambers P, et al. Predictive biomarkers of chemotherapy efficacy in colorectal cancer: results from the UK MRC FOCUS trial. J Clin Oncol. 2008; 26(16): 2690–2698, doi: 10.1200/JCO.2007.15.5580, indexed in Pubmed: 18509181.
17. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res. 2014; 20(20): 5322–5330, doi: 10.1158/1078-0432.CCR-14-0332, indexed in Pubmed: 25139339.
18. Kopetz S, Desai J, Chan E, et al. Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. J Clin Oncol. 2015; 33(34): 4032–4038, doi: 10.1200/JCO.2015.63.2497, indexed in Pubmed: 26460303.
19. Prahallad A, Sun C, Huang S, et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature. 2012; 483(7387): 100–103, doi: 10.1038/nature10868, indexed in Pubmed: 22281684.
20. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. 2015; 373(8): 726–736, doi: 10.1056/NEJMoa1502309, indexed in Pubmed: 26287849.
21. Yaeger R, Cercek A, O'Reilly EM, et al. Pilot trial of combined BRAF and EGFR inhibition in BRAF-mutant metastatic colorectal cancer patients. Clin Cancer Res. 2015; 21(6): 1313–1320, doi: 10.1158/1078-0432.CCR-14-2779, indexed in Pubmed: 25589621.
22. Atreya C, Cutsem EV, Bendell J, et al. Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E mutated (BRAFm) metastatic colorectal cancer (mCRC). J Clin Oncol. 2015; 33(15_suppl): 103–103, doi: 10.1200/jco.2015.33.15_suppl.103.
23. van Geel RM, Tabernero J, Elez E, et al. A phase ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic -mutant colorectal cancer. Cancer Discov. 2017; 7(6): 610–619, doi: 10.1158/2159-8290.CD-16-0795, indexed in Pubmed: 28363909.
24. Yang H, Higgins B, Kolinsky K, et al. Antitumor activity of BRAF inhibitor vemurafenib in preclinical models of BRAF-mutant colorectal

cancer. Cancer Res. 2012; 72(3): 779–789, doi: 10.1158/0008-5472.CAN-11-2941, indexed in Pubmed: 22180495.
25. Kopetz S, McDonough S, Morris V, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG 1406). J Clin Oncol. 2017; 35(4_suppl): 520–520, doi: 10.1200/jco.2017.35.4_suppl.520.
26. Kopetz S, Grothey A, Tabernero J, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med. 2019; 381(17): 1632–1643, doi: 10.1056/NEJMoa1908075, indexed in Pubmed: 31566309.
27. Kopetz S, Grothey A, Cutsem EV, et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E metastatic colorectal cancer: Updated survival results from a randomized, three-arm, phase III study versus choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC). J Clin Oncol. 2020; 38(15_suppl): 4001–4001, doi: 10.1200/jco.2020.38.15_suppl.4001.
28. Hewish M, Lord CJ, Martin SA, et al. Mismatch repair deficient colorectal cancer in the era of personalized treatment. Nat Rev Clin Oncol. 2010; 7(4): 197–208, doi: 10.1038/nrclinonc.2010.18, indexed in Pubmed: 20177404.
29. Parsons MT, Buchanan DD, Thompson B, et al. Correlation of tumour BRAF mutations and MLH1 methylation with germline mismatch repair (MMR) gene mutation status: a literature review assessing utility of tumour features for MMR variant classification. J Med Genet. 2012; 49(3): 151–157, doi: 10.1136/jmedgenet-2011-100714, indexed in Pubmed: 22368298.
30. Smyrk TC, Watson P, Kaul K, et al. Tumor-infiltrating lymphocytes are a marker for microsatellite instability in colorectal carcinoma. Cancer. 2001; 91(12): 2417–2422, indexed in Pubmed: 11413533.
31. Cohen R, Buhard O, Cervera P, et al. Clinical and molecular characterisation of hereditary and sporadic metastatic colorectal cancers harbouring microsatellite instability/DNA mismatch repair deficiency. Eur J Cancer. 2017; 86: 266–274, doi: 10.1016/j.ejca.2017.09.022, indexed in Pubmed: 29055842.
32. Rosenbaum MW, Bledsoe JR, Morales-Oyarvide V, et al. PD-L1 expression in colorectal cancer is associated with microsatellite instability, BRAF mutation, medullary morphology and cytotoxic tumor-infiltrating lymphocytes. Mod Pathol. 2016; 29(9): 1104–1112, doi: 10.1038/modpathol.2016.95, indexed in Pubmed: 27198569.
33. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015; 372(26): 2509–2520, doi: 10.1056/NEJMoa1500596, indexed in Pubmed: 26028255.
34. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017; 357(6349): 409–413, doi: 10.1126/science.aan6733, indexed in Pubmed: 28596308.
35. Andre T, Shiu KK, Kim T, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: The phase 3 KEYNOTE-177 Study. J Clin Oncol. 2020; 38(18_suppl): LBA4–LBA4, doi: 10.1200/jco.2020.38.18_suppl.lba4.
36. Lenz HJ, Lonardi S, Zagonel V, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Two-year clinical update. J Clin Oncol. 2020; 38(15_suppl): 4040–4040, doi: 10.1200/jco.2020.38.15_suppl.4040.
37. Hong DS, Fakih MG, Strickler JH, et al. KRAS Inhibition with Sotorasib in Advanced Solid Tumors. N Engl J Med. 2020; 383(13): 1207–1217, doi: 10.1056/NEJMoa1917239, indexed in Pubmed: 32955176.