Treatment of Unresectable and Resectable Stage IV Colorectal Cancer

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Abstract: Colorectal cancer is the third most commonly diagnosed cancer in the United States. Approximately 20% of patients have metastatic disease at diagnosis, and a proportion of patients with initially localized disease will experience systemic disease recurrence. In the era of molecular subtyping, we have an increasing number of systemic therapies and the opportunity to individualize the treatment of patients with advanced disease. Nonetheless, the 5-year overall survival rate remains unsatisfactory for this patient population. Most patients will be treated with palliative cytotoxic therapy, often with an added monoclonal antibody. Molecular subtyping allows patients to receive targeted therapies upon further lines of therapy. A small portion of patients will have oligometastases that may be amenable to resection or locoregional therapies to help improve outcomes with systemic therapy. Here, we review the current treatment of patients with unresectable and resectable stage IV colorectal cancer, with a focus on pharmacologic therapies.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the United States, affecting an estimated 106,590 people in 2024.[1] Approximately 20% of patients have metastatic disease at diagnosis, which has a 5-year overall survival (OS) rate of 10% to 15% and can make treatment decisions challenging for clinicians.[2,3] For most patients, metastatic CRC (mCRC) is not curable, and the main treatment goals are to extend survival and alleviate symptoms. The introduction of molecular profiling has shifted the treatment paradigm in recent years, opening more treatment options for patients and allowing personalization of therapy. Furthermore, the introduction of combination chemotherapy, immunotherapy, and targeted therapy has improved OS for those with mCRC.[3]

Systemic Therapies

The goal of systemic cytotoxic therapy in the metastatic setting is to

prolong survival without significant toxicity or a decrease in quality of life. Patient fitness, medical conditions, *RAS*/*BRAF* and other mutation status, microsatellite instability (MSI), DNA mismatch repair (MMR) status, and primary tumor location are all factors that are considered in the treatment decision-making process. The choice of initial therapy depends first on whether immunotherapy is an option, and then on the *KRAS* and *BRAF* oncogene mutation status. Because only approximately 5% of patients with mCRC qualify for immunotherapy, this option is discussed later in the review.

Initial (Frontline) Therapies

Doublet Cytotoxic Regimens. The current standard of care for mCRC is 3 active systemic therapies. The backbone is a fluoropyrimidine plus either oxaliplatin or irinotecan, followed by an anti–vascular endothelial growth factor receptor (VEGFR) antibody or an anti–epidermal growth factor receptor (EGFR) antibody, depending on the *KRAS*/*BRAF* mutation status and whether the primary tumor is located on the left or right side.

Doublet cytotoxic therapy improves OS in comparison with fluoropyrimidine monotherapy and provides significantly superior progression-free survival (PFS). Standard doublet regimens include leucovorin, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX); capecitabine and oxaliplatin (CAPOX or XELOX); and leucovorin, 5-FU, and irinotecan (FOLFIRI). Researchers have compared FOLFIRI followed by FOLFOX vs the reverse sequence, and both sequences achieved prolonged survival with similar efficacy.[4] However, the toxicities differ between the 2 regimens. FOLFOX is associated with increased rates of neuropathy and neutropenia, and FOLFIRI is associated with increased rates of gastrointestinal toxicity and mucositis.[4,5] In the elderly or unfit population, single-agent therapy with a fluoropyrimidine is used to avoid the significant toxicity associated with the addition of either oxaliplatin or irinotecan.[6]

Triplet Cytotoxic Regimens. The addition of a third cytotoxic agent, with leucovorin, 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI), is another option for upfront therapy. Studies have shown a significant improvement in response rates, PFS, and overall survival (OS) in patients who received FOLFOXIRI, but with higher rates of neurotoxicity, neutropenia, stomatitis, and diarrhea.[7-9]

The TRIBE study investigated FOLFOXIRI plus bevacizumab as first-line treatment.[10,11] Phase 3 data from this study compared FOLFIRI plus bevacizumab (control) with FOLFOXIRI plus bevacizumab (experimental) in the first-line metastatic setting for up to 12 cycles, followed by 5-FU plus bevacizumab maintenance until progression. The median PFS was 12.1 months in the FOLFOXIRI-plus-bevacizumab cohort vs 9.7 months in the FOLFIRI-plus-bevacizumab cohort. An absolute increase in the objective response rate (ORR) was seen in the experimental cohort, with an increase from 53% to 65%. FOLFOXIRI plus bevacizumab did extend the median OS by 5.2 months, but the increase was not statistically significant. The experimental treatment was also superior for those who had *BRAF*-mutated tumors by subgroup analysis. The incidence of grade 3/4 adverse events (AEs) was significantly higher in the FOLFOXIRI-plus-bevacizumab group for diarrhea, stomatitis, and peripheral neuropathy.

Triplet therapy remains a viable option for well-selected patients who are younger, have a good performance status, and have a more aggressive tumor and/or bulky disease requiring major cytoreduction. It also may be applicable in those who have *BRAF*-mutated tumors, as these patients overall have poorer outcomes. Triplet therapy is also a valuable option to be considered in patients requiring conversion of metastases to resectable status.

Second- and Third-Line Therapies

The selection of further lines of systemic therapy depends on preceding chemotherapy exposure(s), overall health and performance status, organ function and residual toxicities (eg, neuropathy), patient preferences, and the timing of disease progression relative to completion of the prior treatment. If the patient has an actionable mutation, targeted therapy is preferred, as will be discussed later.

In August 2023, the US Food and Drug Administration (FDA) approved the combination of trifluridine/tipiracil (Lonsurf, Taiho Oncology) with bevacizumab. Trifluridine/tipiracil monotherapy does offer a prolonged OS of 7.1 months vs 5.3 months with placebo in refractory mCRC, but the benefit is modest. The most common grade 3 AEs for trifluridine/tipiracil monotherapy are neutropenia (38%) and leukopenia (21%).[12]

The phase 3 trial that led to approval of the combination compared trifluridine/tipiracil plus bevacizumab vs trifluridine/tipiracil alone in patients who had received no more than 2 prior chemotherapy treatments.[13] The median OS was 10.8 months in the combination group and 7.5 months in the trifluridine/tipiracil monotherapy group. Grade 3 AEs were reported in 72.4% of the patients in the combination group and 69.5% of those in the monotherapy group, with the most common being neutropenia, nausea, and anemia. The combination of trifluridine/tipiracil and bevacizumab is generally preferred over monotherapy with trifluridine/tipiracil.

The multikinase inhibitor regorafenib (Stivarga, Bayer HealthCare) provides a modest improvement in median OS, which was 6.4 months with regorafenib vs 5.0 months with placebo.[14] Treatment-related AEs occurred in 93% of patients receiving regorafenib, with the most

Table 1. Biomarker-Driven Therapies in mCRC

Biomarker	Trial/Author	Phase	Treatment	Outcomes
HER2	MOUNTAINEER[30]	2	Trastuzumab/tucatinib	ORR: 38.1% CR: 3 pts
	DESTINY-CRCO1[31]	2	Trastuzumab deruxtecan (T-DXd)	ORR: 45.3% PFS: 6.9 mo OS: 15.5 mo
BRAF V600E	BEACON[27]	3	Encorafenib/cetuximab or encorafenib/panitumumab	ORR: 19.5% OS: 9.3 mo
NTRK	NAVIGATE[35-37] (colon cancer cohort)	2	Larotrectinib	ORR: 47% PFS: 5.5 mo OS: 12.5 mo
	ALKA-372-001, STAR-TRK-1, and STARTRK-2 (pooled analysis all tumors)[38]	1/2	Entrectinib	1 response in 4 pts with colon cancer
RET	LIBRETTO-001[40] (colon cancer cohort)	1/2	Selpercatinib	DOR: 9.4 mo for colon cancer cohort
KRAS G12C	KRYSTAL-1[34]	1/2	Adagrasib/cetuximab or adagrasib/panitumumab	ORR: 34% PFS: 6.9 mo OS: 15.9 mo
	CodeBreaK 101[33]	1b/2	Sotorasib/panitumumab	ORR: 30% PFS: 5.7 mo OS: 15.2 mo
VEGF 1,2,3	FRESCO-2[15]	3	Fruquintinib	OS: 7.4 mo
Tumor mutational burden	TAPUR (colorectal cohort)[43]	2	Pembrolizumab	DCR: 31% ORR: 11%

CR, complete response; DCR, disease control rate; DOR, duration of response; mCRC, metastatic colorectal cancer; mo, months; OR, overall response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pts, patients.

common grade 3 events being hand/foot disease, fatigue, and diarrhea. Starting regorafenib at a lower dose than the FDA-approved dose of 160 mg/d increases the tolerability.

Fruquintinib (Fruzaqla, Takeda) is a highly selective inhibitor of VEGFR 1, 2, and 3. Most patients in the phase 3 trial that led to its approval (Table 1) had seen 3 to 4 prior lines of treatment. Median OS was 7.4 months in the fruquintinib group vs 4.8 months in the placebo group. Grade 3 or higher AEs occurred in 63% of patients who received fruquintinib, with the most common grade 3 or worse events being hypertension, asthenia, and hand-foot syndrome.[15]

There is a void of effective therapies beyond the second line, at which point enrolling patients in clinical trials must be strongly considered.

Predictive Biomarkers and Targeted Therapies

We are well into an era in which molecular subtyping is increasingly driving therapeutic decisions for patients with mCRC, allowing treatment to be tailored for maximum benefit in each patient. *RAS*/*RAF*, *HER2*, and MSI/MMR-deficient (dMMR)/tumor mutational burden (TMB) status is determined universally in most patients with mCRC. The performance of DNA next-generation sequencing (NGS) via plasma or tissue allows the detection of additional mutations that are less commonly seen. Immunohistochemistry (IHC) and RNA sequencing expand the molecular profiling further. Current guidelines recommend therapy with any of the available targetable mutations beyond first-line therapy, and increasingly in the upfront therapy of metastatic or recurrent disease.

MSI and/or dMMR

Although only 5% of patients with mCRC harbor MSI-high (MSI-H)/dMMR tumors, this test has become mandatory in mCRC.[16] It allows testing for Lynch syndrome, and the biomarker has a predictive role in treatment with immune checkpoint inhibitors. Testing is achieved with 3 main methods: polymerase chain reaction (PCR), which is the gold standard and requires a tumor tissue sample; IHC; and NGS. Assessment of the TMB is also recommended.

Incorporation of Anti-EGFR and Anti-VEGF/VEGFR Therapies

RAS mutations occur in 30% to 50% of mCRC tumors, with the most common being *KRAS* mutations in exons 2, 3, or 4.[17] Several studies have shown that patients with tumors that have *RAS* mutations derive no benefit from anti-EGFR–directed therapies.[18] Mutations in *BRAF* are seen in approximately 10% of mCRC tumors. They are most commonly *BRAF* V600E mutations, and *BRAF* mutations and *RAS* mutations are mutually exclusive. *BRAF* mutations may also be associated with MSI-H/dMMR status, with close to half of patients harboring *BRAF* mutations. Like patients with *RAS* mutations, those with *BRAF* mutations are resistant to anti-EGFR–based therapies.[19,20]

The addition of anti-VEGF/VEGFR or anti-EGFR therapy to chemotherapy has been shown to improve survival, with small increases in toxicity. For patients to gain the most benefit from EGFR inhibition, they must have tumors that are *RAS/RAF* wild-type and located on the left side, which includes the splenic flexure, sigmoid colon, and rectum. The addition of cetuximab (Erbitux, Lilly) to FOLFIRI in *RAS/RAF* wild-type tumors improved the median OS from 20 months to 23.5 months and increased response rates from 39.7% to 57.3%.[21] The addition of panitumumab (Vectibix, Amgen) to FOLFOX improved the median OS from 19.7 months to 23.9 months and increased the median PFS from 8.6 to 10.0 months.[22] The PARADIGM randomized clinical trial compared the addition of anti-EGFR and anti-VEGF to 5-FU and oxaliplatin combination chemotherapy in patients with *RAS* wild-type, left-sided mCRC.[23] In patients with left-sided tumors, the median OS was 37.9 months with panitumumab and FOLFOX vs 34.3 months with bevacizumab and FOLFOX. These improvements were modest and did not add major toxicity in comparison with chemotherapy alone. In practice, cetuximab and panitumumab are used interchangeably. A systematic review and meta-analysis comparing the use of cetuximab vs panitumumab for EGFR inhibition in patients with *RAS* wild-type tumors showed no significant difference between the 2 drugs in median PFS, median OS, or response rate. Also, no significant difference was noted in the incidence of acneiform rash and diarrhea, making either one a reasonable choice.[24]

Current FDA approved anti-VEGF/VEGFR therapies include bevacizumab, ziv-aflibercept (Zaltrap, Sanofi/Regeneron), and ramucirumab (Cyramza, Lilly). They are given in combination with irinotecan- or oxaliplatin-containing chemotherapy regimens and can be given regardless of the primary tumor side or *RAS/RAF* mutation status. When combined with irinotecan-containing chemotherapy (FOLFIRI), the median OS was 20.3 months and the median PFS was 10.6 months in the group given FOLFIRI plus bevacizumab vs a median OS of 15.6 months and a median PFS of 6.2 months in the group given FOLFIRI alone. The incidence of hypertension was increased with bevacizumab, but this was easily managed.[25] When bevacizumab was added to oxaliplatin-containing regimens (FOLFOX), the median OS was 12.9 months in the group treated with chemotherapy and bevacizumab vs 10.8 months in the group treated with chemotherapy alone. The median PFS was 7.3 months for those treated with the combination of bevacizumab and FOLFOX and was 4.7 months for those treated with FOLFOX alone.[26] Bevacizumab was associated with delayed wound healing and an increased risk of bleeding, which must be taken into consideration if therapy is to be initiated around surgery.

For those patients with *BRAF* V600E mutations, initial chemotherapy is less effective, and the patients have worse OS. The combination of an anti-EGFR therapy with an anti-BRAF agent has shown improved benefit because of blockage of the feedback stimulatory signaling through *EGFR*. In the phase 3 BEACON trial, patients were randomized to receive a triplet combination of encorafenib (Braftovi, Pfizer), binimetinib (Mektovi, Pfizer), and cetuximab (BRAF, MEK, and EGFR inhibition, respectively); a doublet combination of encorafenib and cetuximab; or a control regimen of cetuximab plus either irinotecan or FOLFIRI. Median OS times were 5.9 months, 9.3 months, and 9.3 months, respectively. The triplet arm showed no advantage over the doublet and had more toxicity, findings that led to FDA approval of the doublet. In today's practice, those whose disease fails to respond to first-line chemotherapy and have a *BRAF* V600E mutation are given doublet therapy with encorafenib plus either cetuximab or panitumumab.[27]

The current guidelines recommend the use of anti-EGFR therapy in addition to chemotherapy as first-line treatment in patients with mCRC who have *RAS/RAF* wild-type and left-sided tumors. Anti-VEGF therapy added to chemotherapy as first-line therapy is recommended in patients who have right-sided and *RAS/RAF* wild-type tumors. If anti-EGFR therapy is not available or suitable, anti-VEGF therapy can also be used in left-sided tumors, although the benefit is not as impressive as with anti-EGFR therapy in this population. In *RAS/RAF*-mutated tumors, anti-VEGF therapy can also be utilized, whereas EGFR therapy shows no benefit.[28] If a *BRAF* V600E mutation is present, this is usually targeted after failure of first-line chemotherapy.

HER2 *Amplification/Overexpression*

Human epidermal growth factor receptor 2 (*HER2*) amplification and overexpression is reported in approximately

2% to 5% of all cases of mCRC. Its prevalence has been noted to be elevated in *RAS/RAF* wild-type tumors and in left-sided colon cancers. Its role as a prognostic marker is still unclear, although *HER2* amplification predicts resistance to EGFR-targeted therapy.[29] In patients who have *HER2*-amplified disease that is *RAS/RAF* wild-type and has failed to respond to at least first-line chemotherapy, current FDA-approved options include monotherapy with trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca) or combination therapy with trastuzumab plus tucatinib (Tukysa, Seagen). Although the combination is not approved by the FDA at this time, additional data exist for trastuzumab plus pertuzumab (Perjeta, Genentech) or lapatinib.

The combination of trastuzumab and tucatinib was studied in the phase 2 MOUNTAINEER trial. MOUNTAINEER was initially a single-arm phase 2 study in which all patients were treated with trastuzumab and tucatinib. After a protocol amendment, some patients were randomized to tucatinib monotherapy and others received the combination therapy.[30] For those who received the combination therapy of trastuzumab and tucatinib, the overall response rate (ORR) was 38.1%, with 3 patients achieving a complete response. The responses were numerically lower in the patients treated with single-agent tucatinib. Diarrhea was the most common side effect in all cohorts. This trial led to the approval of tucatinib for *HER2*-amplified mCRC.

T-DXd, an HER2-directed antibody conjugated with a topoisomerase I inhibitor, was studied in the phase 2 DESTINY-CRC01 trial. This study included patients whose disease had progressed on at least 2 prior regimens (including HER2-directed therapy) and who were *RAS* wild-type. This trial had 3 cohorts: (A) IHC 3+ or IHC 2+/in situ hybridization (ISH)+; (B) IHC 2+/ISH–; and (C) IHC 1+. No responses occurred in cohorts B and C. Results from cohort A showed an ORR of 45.3%. The median PFS was 6.9 months and the median OS was 15.5 months in this cohort.[31] The most common grade 3 AEs were anemia and neutropenia. Interstitial lung disease developed in 8 patients, with 3 deaths from this complication.

The DESTINY-CRC02 trial (NCT04744831) is ongoing and includes patients who are *HER2*-amplified and either *RAS* wild-type or *RAS*-mutated. Preliminary results are showing activity in both cohorts irrespective of *RAS* mutation status and activity in those who previously received HER2-directed therapy.[32]

KRAS *G12C Mutation*

Patients with a *KRAS* G12C mutation whose disease has failed to respond to first-line treatment may benefit from targeted therapy with an oral *KRAS* G12C inhibitor in combination with an EGFR inhibitor. The phase 1b/2 CodeBreaK 101 trial looked at the combination of sotorasib (Lumakras, Amgen) and panitumumab in 40 previously treated patients with a *KRAS* G12C mutation.[33] The results showed an ORR of 30%. The median PFS and OS were 5.7 and 15.2 months, respectively. Grade 3 or higher AEs occurred in 27% of the patients.

Results from the phase 1/2 KRYSTAL-1 trial, in which 94 patients who had mCRC with a *KRAS* G12C mutation received adagrasib (Krazati, Mirati Therapeutics) and cetuximab, showed an ORR of 34.0%. The median PFS was 6.9 months and the median OS was 15.9 months. Grade 3/4 AEs occurred in 27.7% of patients, with the most common being rash, acneiform dermatitis, and hypomagnesemia.[34] None led to adagrasib discontinuation. This combination gained FDA approval in June 2024.

NTRK *Fusions*

Studies estimate that *NTRK* fusions are found in approximately 1% or fewer of patients with mCRC, with most of these tumors also being dMMR.[35] Current FDA-approved *NTRK* fusion inhibitors include larotrectinib (Vitrakvi, Bayer), entrectinib (Rozlytrek, Genentech), and repotrectinib (Augtyro, Bristol Myers Squibb) for use in the second-line setting or beyond. An expanded data set for larotrectinib from the NAVIGATE trial analyzed gastrointestinal cancers, with 19 patients having mCRC.[35-37] The ORR was 47%, with a median PFS of 5.5 months and a median OS of 12.5 months. Larotrectinib was well tolerated; most of the AEs were increased alanine transaminase (ALT) or aspartate transaminase (AST), and nausea was grade 1 or grade 2. The efficacy of entrectinib was shown in an integrated pooled analysis of 3 phase 1/2 trials (ALKA-372-001, STARTRK-1, and STARTRK-2) in a total of 54 patients with advanced or metastatic *NTRK* fusion–positive solid tumors.[38] Of the 4 patients with colon cancer, 1 had a response. Most AEs were also grade 1 or 2; a few of the most common events were dysgeusia, diarrhea/constipation, and fatigue. Repotrectinib (a multikinase inhibitor of *ROS1* and *TRK* fusion proteins) has recently gained FDA approval from the phase 1/2 TRIDENT-1 trial.[39] The ORR for all solid tumors in the tyrosine kinase inhibitor (TKI)–naive group was 56%, and the 12-month PFS rate was 56%. In the TKI-pretreated cohort for all solid tumors, the ORR was 50% and the 12-month PFS rate was 22%. Grade 3 AEs occurred in 51% of patients, with dizziness the most common. Subgroup analysis data for mCRC are not yet available, but repotrectinib remains an option.

RET *Mutations*

RET mutations are very rare in colon cancer. Selpercatinib

Table 2. Immunotherapy Studies in Patients With mCRC and MSI-H/dMMR

Trial	Phase	Treatment	Line of Therapy	Outcomes
KEYNOTE-177[44]	3	Pembrolizumab	First	ORR: 43.8% PFS: 16.5 mo
CheckMate 142[47]	2	Nivolumab	First	ORR: 31.1% DCR ≥12 wk: 69%
CheckMate 142[47]	2	Nivolumab/ipilimumab	First	ORR: 71% 60-mo PFS rate and OS rate, respectively: 55% and 67%
CheckMate 8HW abstract[48]	3	Nivolumab/ipilimumab	First	79% reduction in progression or death
GARNET[49]	1	Dostarlimab	First	ORR: 43.5% PFS: 8.4 mo

DCR, disease control rate; dMMR, mismatch repair–deficient; mCRC, metastatic colorectal cancer; mo, months; MSI-H, microsatellite instability–high; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; wk, weeks.

(Retevmo, Lilly), a RET inhibitor, is FDA-approved for colon cancer after the failure of first-line systemic chemotherapy. The phase 1/2 LIBRETTO-001 trial was a basket trial that included all patients with *RET*-mutated cancers. In the colon cancer cohort, the median duration of response was 9.4 months and the safety profile was reasonable, making selpercatinib a viable option for this patient population.[40]

Tumor Mutational Burden

TMB, defined as the number of somatic mutations per megabase of interrogated genomic sequence, demonstrates potential as a predictive biomarker for the identification of patients with cancer who are most likely to respond to immune checkpoint inhibitors.[41] The FDA has approved pembrolizumab (Keytruda, Merck) for previously treated solid tumors that are TMB-high (TMB-H), which was defined as at least 10 mutations per megabase.[42] The use of pembrolizumab in patients with TMB-H colon cancer was studied in a cohort from the TAPUR registry trial. This study defined TMB-H as at least 9 mutations per megabase and the analysis included 27 patients with advanced CRC who had been pretreated and had no other standard treatment options.[43] Results showed a disease control rate of 31% and an ORR of 11%. Pembrolizumab monotherapy is a reasonable option in heavily pretreated patients with TMB-H mCRC.

Immunotherapy

Although only about 5% of patients with mCRC have MSI-H or dMMR tumors, immunotherapy is now an established therapeutic strategy for first-line or subsequent-line treatment in this patient population (Table 2). In general, these patients have a poor response to conventional cytotoxic therapy. Currently approved immunotherapy for patients with dMMR/MSI-H tumors or polymerase ε (*POLE*)/polymerase δ1 (*POLD1*) mutations includes pembrolizumab, nivolumab (Opdivo, Bristol Myers Squibb) with or without ipilimumab (Yervoy, Bristol Myers Squibb), and dostarlimab (Jemperli, GlaxoSmithKline).

Pembrolizumab

Pembrolizumab is a monoclonal antibody that binds to programmed death 1 (PD-1), thereby enhancing the immune system response to the tumor. The pivotal phase 3 KEYNOTE-177 trial compared single-agent pembrolizumab with chemotherapy (investigator's choice) in MSI-H/dMMR mCRC in the first-line setting. In the study, 60% of patients crossed over from chemotherapy to anti–PD-1/anti–programmed death ligand 1 (PD-L1) therapy. The ORR was 43.8% in the pembrolizumab arm. Median PFS was 16.5 months in the pembrolizumab cohort vs 8.2 months in the chemotherapy cohort.[44] Median OS was not reached in the pembrolizumab group, although in a post hoc analysis, the 36-month median OS was 61.4% in the pembrolizumab group vs 50.3% in the chemotherapy treated patients. Grade 3 adverse events occurred in 22% of patients in the pembrolizumab arm, with the most common being transaminitis, colitis, diarrhea, and fatigue.

Nivolumab and/or Ipilimumab

Nivolumab is approved by the FDA as monotherapy or in combination with ipilimumab for MSI-H or dMMR mCRC as first-line treatment, per the phase 2 CheckMate 142 trial.[45,46] Nivolumab is a PD-1 inhibitor and ipilimumab is a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor. Nivolumab monotherapy was studied in a total of 74 patients, 40 of whom had received 3 or more lines of treatments. A total of 31.1%

of patients achieved an objective response, and 69% of patients had disease control for at least 12 weeks. For the nivolumab-plus-ipilimumab cohort, the ORR was 69%, with a disease control rate of 84% at a 29-month follow-up. Updated 64-month follow-up of combination therapy with nivolumab plus ipilimumab showed an ORR of 71%.[47] The median PFS and median OS were not reached, with a 60-month PFS rate of 55% and an OS rate of 67%.

The phase 3 CheckMate 8HW trial compared nivolumab/ipilimumab with chemotherapy in the first-line setting.[48] Patients received nivolumab (240 mg) plus ipilimumab (1 mg/kg) every 3 weeks for 4 cycles followed by nivolumab (480 mg) every 4 weeks. At a median follow-up of 24.3 months, the nivolumab/ipilimumab combination showed a statistically significant improvement in PFS and a 79% reduction in the risk of progression or death. The patients treated with nivolumab plus ipilimumab had a lower rate of grade 3 or higher treatment-related AEs vs the patients who received chemotherapy (23% vs 48%). OS data are pending.

Dostarlimab

Dostarlimab-gxly is an FDA-approved PD-1 inhibitor for patients with dMMR/MSI-H tumors. The phase 1 GARNET trial enrolled patients with advanced or recurrent dMMR, MSI-H, or *POLE*-altered solid tumors.[49] Of the 327 patients enrolled, 115 had dMMR, MSI-H, or *POLE*-altered colon cancer. The ORR for the colon cancer population was 43.5%, and 12.2% achieved a complete response. The median PFS was 8.4 months; the median duration of response and median OS were not yet reached. Grade 3 AEs occurred in 16.3% of the total number of patients enrolled in this trial, with the most common being hypothyroidism, ALT increase, and arthralgias.

Regional Therapies

For some patients with mCRC, especially those with oligometastatic disease, multimodal treatment strategies with a curative intent will have a role. Regional therapy must always be considered in well-selected patients who have been exposed to initial systemic therapy and experienced a favorable response.

Surgical resection remains the preferred approach for patients who have resectable liver metastasis and offers a chance of cure in this population. Retrospective analyses and meta-analyses have shown that patients with a solitary liver metastasis may have a 5-year median OS nearing 72% following resection.[50] Tumor ablation can be used in patients with liver or lung oligometastases, particularly those that cannot be resected. Although radiofrequency ablation is inferior to surgical resection, evidence indicates that this is a reasonable option for patients who are not surgical candidates. Tumor ablation is also commonly used for small recurrent hepatic metastases if a clear margin can be achieved.[51-53] External beam radiation therapy (EBRT) can also be considered in patients with limited metastatic sites in the liver or lung. In general, this is well tolerated and effective for local tumor control.[54,55]

Hepatic arterial infusion pump (HAIC) requires the surgical placement of a hepatic arterial port or implantable pump, followed by the infusion of floxuridine (FUDR) into the hepatic artery. Several studies have shown improved response rates in comparison with systemic therapy, but many of the studies were not powered for survival data.[56] A meta-analysis showed improved response rates and a higher OS rate without a difference in median PFS.[57] This modality can be used in selected patients to downstage liver metastasis for resection and/or provide durable disease control in the liver.[58]

In yttrium 90 radioembolization, ^{90}Y resin microspheres are directed at liver metastases. A combined analysis examined data from randomized phase 3 trials—FOXFIRE, SIRFLOX, and FOXFIRE-Global—in which patients were randomized either to FOLFOX systemic chemotherapy or to FOLFOX plus single-treatment selective internal radiotherapy with ^{90}Y resin microspheres.[59] No difference in survival was noted, and data regarding survival benefit for this therapy are limited.

Recent data from the randomized, prospective TRANSMET trial compared the efficacy of adding liver transplant to chemotherapy vs the efficacy of chemotherapy alone in patients with definitively unresectable liver metastases.[60] Patients who had resected *BRAF* wild-type colon cancer that responded to chemotherapy for at least 3 months and did not have extrahepatic disease were randomized to receive liver transplant and chemotherapy or chemotherapy alone. In the intention-to-treat analysis, the 5-year median OS rate was 57% and the median PFS was 17.4 months in the liver transplant-plus-chemotherapy cohort. The 5-year median OS rate was 13% and the median PFS was 6.4 months in the chemotherapy-only cohort. These results suggest a new possible standard-of-care consideration for patients with liver-only metastatic disease.

Personalizing Therapy and the Role of Maintenance Treatment

After initial induction therapy with either FOLFOX or FOLFIRI, more than 50% of patients will have a partial or complete response or at least exhibit stable disease. The continuation of chemotherapy over an extended period becomes limited by cumulative side effects in most

patients. A typical maintenance therapy approach starts with induction multiagent therapy followed by less-intensive treatment with 1 to 2 drugs.[61] Several trials have investigated the benefits of maintenance therapy with differing strategies vs observation after initial induction in patients who had at least stable disease without progression. The phase 3 CAIRO3 study from the Netherlands compared capecitabine plus bevacizumab vs observation in previously untreated patients who had stable disease after induction with 6 cycles of CAPOX and bevacizumab. Maintenance with capecitabine and bevacizumab improved PFS to 11.7 months vs 8.5 months in the observation group, without a significant effect on quality of life.[62] Another phase 3 trial compared single-agent capecitabine as maintenance vs observation in patients who had received CAPOX or FOLFOX for induction. Capecitabine alone improved PFS to 6.43 months from 3.43 months in the observation arm, with similar safety profiles in both arms.[63] A trend toward longer median OS was observed in the capecitabine maintenance group vs the observation group, but the difference was not statistically significant (25.63 vs 23.3 months).

A systematic review and network meta-analysis of 12 relevant randomized clinical trials found that continuing full cytotoxic chemotherapy until progression, without maintenance or an observation period, is not beneficial. Maintenance therapy does improve the median PFS, although not the median OS. In general, these therapies are also well tolerated, making them a viable and reasonable treatment option for appropriate patients.[61]

Conclusion

Molecular profiling is crucial for every patient who has mCRC to help guide treatment decisions upfront, and it also can be used to guide later lines of therapy, provide a better understanding of each patient's tumor biology/prognosis, and prevent toxicity from therapies that will not be effective for a given patient. Systemic chemotherapy, targeted therapies, immunotherapy, and multimodal therapies all extend survival for most patients. Ongoing research is needed to continue to move forward, with the goal of helping these patients live longer.

Disclosures

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