Clinical Trials and Progress in Metastatic Colon Cancer

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KEYWORDS

• Colorectal cancer • Clinical trials • KRAS • BRAF • Her2 • Immunotherapy

KEY POINTS

- Presence of mutations in KRAS, NRAS, or BRAF and potentially amplifications in Her2 should be used to guide the use of anti–endothelial growth factor receptor therapies for patients with metastatic colorectal cancer.
- The elucidation of several molecular alterations in metastatic colorectal cancer, including KRAS, NRAS, BRAF, Her2, cMET, mismatch repair, and others, are guiding drug development, clinical trials, and individualized therapy for patients with metastatic colorectal cancer.
- Beyond the rise of immunotherapy for patients with mismatch repair deficiency–related colorectal cancer, several other novel immunotherapy strategies are being evaluated.

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related deaths worldwide but mortality associated with this disease has declined in recent decades due to improved screening, better surgical techniques enabling resection of both local and metastatic disease in more patients, improved preoperative and postoperative care, and more effective systemic therapies across all stages of the disease.[1–3] The availability of fluoropyrimidines (5-fluorouracil and capecitabine), oxaliplatin, and irinotecan as the backbones of therapy for metastatic disease has resulted in median overall survival (OS) of up to 24 months.[4] With the addition of agents inhibiting angiogenesis via targeting vascular endothelial growth factor (VEGF) (bevacizumab, ramucirumab, and ziv-aflibercept) and agents inhibiting the epidermal growth factor receptor (EGFR)

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signaling pathway (cetuximab and panitumumab), median survival has risen to 30 months in the RAS wild-type patient population.[4] More recently, 2 agents, regorafenib (a broad-spectrum multikinase inhibitor) and trifluridine/tipiracil (a fluoropyrimidine compound), have added to the armamentarium in the salvage setting.

CRC was one of the first tumors to undergo comprehensive genomic characterization that demonstrated several genes and pathways implicated in the disease's development and progression.[5–8] It has transformed CRC into a disease of genomic/transcriptomic subtypes. Additionally the field has recognized that tumors undergo genomic/molecular evolution while under treatment. Critical pathways include TP53, BRAF, KRAS, Her2, PIK3CA, APC, transforming growth factor (TFG)-β, CTNNB and WNT signaling, epithelial-to-mesenchymal transition, MYC amplification, mismatch repair (MMR), and others.[9]

Based on this work, several molecular classifications have arisen, although there are differences among them and none has emerged as a standard in clinical practice.[8,10–17] One such classification system, the consensus molecular subtypes (CMSs), was developed from a comprehensive effort of the CRC Subtyping Consortium. Recognizing that transcriptomics is closely linked to tumor phenotype and clinical behavior, they sought to characterize, in a common set of samples, the key biological features of core subtypes while integrating all other available data sources (mutation, copy number, methylation, microRNA, and proteomics) and assessing correlations with patient outcome.[18] The subtypes developed were the following: CMS1 (microsatellite instability immune) characterized by a hypermutated, microsatellite unstable and strong immune activation state; CMS2 (canonical) characterized by epithelial nature with marked WNT and MYC signaling activation; CMS3 (metabolic) characterized by epithelial nature and evident metabolic dysregulation; and CMS4 (mesenchymal) characterized by prominent TGF-β activation, stromal invasion, and angiogenesis. On integration with clinical data, CMS1 tumors were noted to be more frequently diagnosed in women with right-sided lesions, presenting more often with higher histopathologic grade; CMS2 tumors were mainly left-sided; CMS4 tumors tended to be diagnosed at more advanced stages (III and IV). Analysis of combined data sets, and additionally in a subset of patients from the PETACC-3 clinical trial, revealed that CMS4 tumors resulted in decidedly worse OS and worse relapse-free survival. Conversely, superior survival rates after relapse were seen in CMS2 patients, with a larger proportion of long-term survivors in this subset. The CMS1 population had a poor survival rate after relapse.[14,18,19]

Also of emerging importance, and likely rooted in differences in embryologic origin and associated molecular variances, is the role of primary tumor location—right colon versus left colon—as predictive and prognostic subtypes in metastatic CRC.[20] In at least 2 large analyses, tumors arising in the right colon versus left colon were clinically different, with left-sided primary tumors having superior OS and progression-free survival (PFS) compared with right-sided tumors.[20,21] This difference in location was independently predictive in the face of multiple molecular parameters analyzed, including CMS subtypes. These developments are in need of incorporation into prospective trials to validate and advance individualized treatment of patients. This, taken together with the presence of several molecular alterations, including KRAS, BRAF, Her2, cMET, MMR, and others, are guiding drug development, clinical trials, and individualized therapy for patients with CRC.

MUTATIONS IN THE RAS PATHWAY AND THEIR IMPLICATIONS ON CHOICE OF THERAPY

The Kirsten Ras (KRAS) oncogene encodes for a guanosine triphosphateguanosine diphosphate binding protein downstream of the EGFR in the RAS/RAF/MAPK