

Advanced Colorectal Cancer

abstr 0817

New Agents on the Horizon: Positioning Them for Advantage

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The past 10 to 15 years have seen considerable advances in the treatment of colorectal cancer, particularly in terms of having three new cytotoxic agents and three targeted agents added to the approved therapies for this disease since 1995, when 5-fluorouracil was the only such option. The role of KRAS mutation status to predict resistance to epidermal growth factor receptor (EGFR)-directed therapies can also be considered an important, useful step. Such selective indicators will help to target treatments more appropriately, with fewer toxicities and lower costs for unnecessary treatments in patients who are unable to benefit from them.

Nevertheless, the clinical benefit yield (ie, patient survival) from having seven approved therapeutic agents has been less than had been hoped for or expected. More meaningful advances in the treatment of colorectal cancer will require a better understanding of its varied molecular underpinnings, and the identification of agents targeting pathways other than EGFR and vascular endothelial growth factor (VEGF), biomarkers for patient selection, and treatment paradigms that position novel and established agents for optimal clinical outcomes.

New agents that are being evaluated in colorectal cancer include RAS/RAF/MEK and cMET tyrosine kinase inhibitors, inhibitors of PI3-kinase/AKT/mTOR pathways, Src inhibitors, anti-cytotoxic T lymphocyte antigen 4 (anti-CTLA4) monoclonal antibodies, and insulin-like growth factor 1 receptor (IGF1R) blockers. Rationale and strategies for evaluation of some of these classes of agents will be discussed.