



Illustration by Erin Moore

# CLINICAL Colorectal Cancer

and Other Gastrointestinal  
Malignancies

Volume 21, Number 3 • September 2022

## Table of Contents

### Commentary

- 175 “Global Multidisciplinary Team Meetings”: Challenging Cases Virtual Forums from the International Multidisciplinary Anal Cancer Conference (IMACC)

*Eva Segelov, Marianne GrOnlie Guren, David Sebag-Montefiore, Sheela Rao, Anders Johnsson, Pierfrancesco Franco, Eric Deutsch, Dirk Arnold, Karen-Lise Garm Spindler*

### Congress Reports

- 188 Highlights from the 2022 ASCO gastrointestinal cancer symposium: An overview by the EORTC gastrointestinal tract cancer group

*Francesco Sclafani, Elisa Fontana, Lucjan Wyrwicz, Anna Dorothea Wagner, Juan W. Valle, Elizabeth Smyth, Mark Peeters, Radka Obermannova, Cindy Neuzillet, Manfred P. Lutz, Thibaud Koessler, Irit Ben-Aharon, Dirk Arnold, Maria Alsina, Markus Moehler*

### Reviews

- 198 Clinical Updates for Colon Cancer Care in 2022

*Jesus C. Fabregas, Brian Ramnarain, Thomas J. George*

### Original Studies

- 204 Intraoperative Radiation After Pelvic Short Course Radiation-Based Total Neoadjuvant Therapy for Patients With Rectal Adenocarcinoma at High Risk for Local Recurrence

*Zooha Khan, Michael K. Rooney, Prajnan Das, Ethan B. Ludmir, Eugene J. Koay, Grace L. Smith, Cullen Taniguchi, Bruce D. Minsky, Albert C. Koong, Gabriel Sawakuchi, Sam Beddar, Rachael M. Martin, Miguel Rodriguez-Bigas, Oliver Peacock, George Chang, Emma B. Holliday*

Intraoperative radiation therapy enables treatment escalation at a threatened/involved margin and may be helpful for patients at high risk of local recurrence. Ten patients with involved or threatened circumferential resection margin at diagnosis received short course radiation-based total neoadjuvant therapy and intraoperative radiation at the time of surgery. Despite high-risk features, none of the 10 patients developed a pelvic recurrence.

- 212 Correlative Significance of Tumor Regression Grade and ypT Category in Patients Undergoing Preoperative Chemoradiotherapy for Locally Advanced Rectal Cancer**  
*Hyo Seon Ryu, Jong Lyul Lee, Chan Wook Kim, Yong Sik Yoon, In Ja Park, Seok-Byung Lim, Chang Sik Yu, Ji Hun Kim, Jin Cheon Kim*  
 With preoperative chemoradiotherapy being used as a standard treatment for locally advanced rectal cancer patients, accurate evaluation of treatment response has been warranted. We investigated the association between tumor regression grade and ypT category in 1240 rectal cancer patients who underwent preoperative chemoradiotherapy, and we found that a worse tumor regression grade was associated with a more advanced ypT stage.
- 220 Prognostic and Predictive Role of Body Mass Index (BMI) in Metastatic Colorectal Cancer (mCRC): A Pooled Analysis of Tribe and Tribe-2 Studies by GONO**  
*Emanuela Dell'Aquila, Daniele Rossini, Alessandro Galletti, Marco Stellato, Alessandra Boccaccino, Veronica Conca, Marco Maria Germani, Francesca Bergamo, Francesca Daniel, Andrea Spagnoletti, Leonardo Provenzano, Gianluca Tomasello, Alberto Zaniboni, Angela Buonadonna, Laura Fanchini, Samanta Cupini, Chiara Carlomagno, Salvatore Caponnetto, Stefania Rapisardi, Daniele Santini*  
 The role of body mass index is unclear in metastatic colorectal cancer patients. We analyzed data from 1160 pts enrolled in TRIBE and TRIBE-2 trials. Our analyses showed that BMI was neither prognostic nor predictive for PFS and OS.
- 229 Long-Term Safety Data on S-1 Administered After Previous Intolerance to Capecitabine-Containing Systemic Treatment for Metastatic Colorectal Cancer**  
*Cornelis J.A. Punt, Johannes J.M. Kwakman, Linda Mol*  
 The oral fluoropyrimidine S-1 has mainly been tested in Asian patients and was shown to be a valid alternative to capecitabine in the treatment of metastatic colorectal cancer. We evaluated the outcome in 47 Western patients who switched from capecitabine to S-1 due to hand-foot syndrome or cardiac toxicity, derived from a prospective cohort study. S-1 was well tolerated in all patients, indicating that S-1 is of special interest for this patient population.
- 236 Safety and Efficacy of Avelumab in Small Bowel Adenocarcinoma**  
*Dana B. Cardin, Jill Gilbert, Jennifer G. Whisenant, Gregory D. Ayers, Florencia Jalikis, Kimberly B. Dahlman, Jamye F. O'Neal, Frank Revetta, Chanjuan Shi, Jordan Berlin*  
 Phase II study explored efficacy of the PD-L1 antibody avelumab in small bowel adenocarcinomas (SBAs). Two patients (2/7; 29%) experienced partial responses and disease-control rate was 71%. Despite the observed benefit, accrual was slower than expected and the study was closed early due to feasibility. Disease rarity and off-label use of immunotherapy were likely drivers of insufficient accrual.
- 244 Encorafenib in Combination With Cetuximab After Systemic Therapy in Patients With BRAF<sup>V600E</sup> Mutant Metastatic Colorectal Cancer: German Health Technology Assessment-Driven Analyses From the BEACON CRC Study**  
*Sebastian Stintzing, Thomas Seufferlein, Christian Rosé, Frank Reichenbach, Diana Lüftner*  
 The German Health Technology Assessment (HTA) helps the clinician by giving an additional evaluation of the clinical evidence of a substance in the light of a risk benefit assessment. In the HTA a "hint for a considerable additional benefit" of encorafenib + cetuximab compared to the ACT in BRAFV600E-mutant mCRC patients was granted. This treatment is considered the new standard of care for these patients.
- 252 A Phase I Clinical Trial of Trametinib in Combination with TAS-102 in Patients with Chemotherapy-Resistant RAS-Mutated (PIK3CA/PTEN-Wild Type) Metastatic Colorectal Cancer**  
*Jeremy Chuang, Jun Gong, Sierra Min Li, Chongkai Wang, Marwan Fakh*  
 Preclinical models have shown synergistic activity between MEK inhibitors and TAS-102 in RAS- mutant and PIK3CA wild-type PTEN + models. In our 3 + 3 dose de-escalation single arm phase I, trametinib in combination with TAS-102 did not achieve meaningful clinical benefit however it did demonstrate a manageable safety profile in this molecularly selected cohort with refractory metastatic colorectal cancer

259 **Germline Polymorphisms in Genes Involved in the Antioxidant System Predict the Efficacy of Cetuximab in Metastatic Colorectal Cancer Patients Enrolled in FIRE-3 Trial**

*Hiroyuki Arai, Joshua Millstein, Yan Yang, Sebastian Stintzing, Jingyuan Wang, Francesca Battaglin, Natsuko Kawanishi, Priya Jayachandran, Shivani Soni, Wu Zhang, Volker Heinemann, Heinz-Josef Lenz*

Although reactive oxygen species are tightly linked to the EGFR/RAS/MAPK signaling pathway, the clinical implications of aberrance in molecules regulating redox balance in metastatic colorectal cancer are unclear. We present the first evidence from a phase III study that an antioxidant-related single-nucleotide polymorphism (TXN2 rs4921494) is associated with the efficacy of cetuximab in metastatic colorectal cancer patients.

## Case Report

267 **Rechallenge With BRAF and anti-EGFR Inhibitors in Patients With Metastatic Colorectal Cancer Harboring BRAF<sup>V600E</sup> Mutation Who Progressed on Cetuximab and Encorafenib With or Without Binimetinib: A Case Series**

*Jingran Ji, Chongkai Wang, Marwan Fakih*

272 **Targeted Fibroblast Growth Factor Receptor (FGFR) Inhibition in Recurrent, Metastatic Anal Carcinoma: A Case Report**

*Kayla W. Miranda, Sarah K. Cimino, Cathy Eng*

**Available Exclusively Online at [www.clinical-colorectal-cancer.com](http://www.clinical-colorectal-cancer.com)**

e148 **Restoring Immune Mediated Disease Control by Ipilimumab Re-exposition in a Heavily pretreated Patient With MSI-H mCRC**

*Frank Jordan, Martin Trepel, Rainer Claus*

e152 **Efficacy and Safety Comparison of Regorafenib and Fruquintinib in Metastatic Colorectal Cancer-An Observational Cohort Study in the Real World**

*Qi Zhang, Mifen Chen, Zhenghang Wang, Changsong Qi, Yanshuo Cao, Junyan Zhang, Zhi Peng, Xicheng Wang, Ming Lu, Lin Shen, Jian Li*

Regorafenib and fruquintinib are tyrosine kinase inhibitors that have been approved in the management of refractory metastatic colorectal cancer (mCRC) in China. However, limited data on the better treatment option has been reported for these mCRC patients. This ambispective observational cohort study evaluated the differences of efficacy and safety between regorafenib and fruquintinib. This study found that regorafenib and fruquintinib had similar efficacy for mCRC patients in a real-world setting. The toxicity profiles of the two drugs were also similar, but the frequency varied. Additionally, regorafenib followed by fruquintinib showed longer overall survival than the reverse, but the sequence needs to be further confirmed.

e162 **Post-induction Strategies in Metastatic Colorectal Cancer Patients Treated With First-Line Anti-EGFR-Based Treatment: A Systematic Review and Meta-Analysis**

*Alessandro Parisi, Michele Ghidini, Riccardo Giampieri, Gianluca Tomasello, Andrea Luciani, Claudio Ferri, Rossana Berardi, Fausto Petrelli*

e171 **Impact of the COVID-19 Pandemic on Colorectal Cancer Care in the Netherlands: A Population-based Study**

*Joyce Meijer, Marloes A.G. Elferink, Jolanda C. van Hoeve, Jeroen Buijsen, Felice van Erning, Iris D. Nagtegaal, Pieter J. Tanis, Geraldine R. Vink, Miriam L. Wumkes, Ignace H.J.T. de Hingh, Sabine Siesling*

The COVID-19 pandemic disrupted health care services worldwide. This study aimed to investigate the impact of the pandemic on colorectal cancer care in the Netherlands. In total, 1,653 colorectal cancer patients diagnosed in 25 hospitals in weeks 2 to 26 of 2020 were selected from the Netherlands Cancer Registry. The impact on colorectal cancer care in the Netherlands was limited.

- e179 **QUAD SHOT Radiotherapy and Doublet Immunotherapy in the Management of Anal Mucosal Melanoma: A Case Series of Efficacy and Toxicity of a Novel Treatment Approach and a Review of the Literature**  
*Martin J. Higgins, Ramin Alipour, Kathy Pope, Kim Ann Ung, David L. Kok, Margaret S-T Chua*
- e187 **Thinking Too Fast About Chemotherapy for Resectable Colorectal Cancer Liver Metastases?**  
*Allan A. Lima Pereira, Gustavo Dos Santos Fernandes*
- e189 **Cost-effectiveness of DPYD Genotyping Prior to Fluoropyrimidine-based Adjuvant Chemotherapy for Colon Cancer**  
*Gabriel A. Brooks, Stephanie Tapp, Allan T. Daly, Jonathan A. Busam, Anna N.A. Tosteson*  
 Fluoropyrimidine chemotherapy agents are widely used in cancer treatment. Dihydropyrimidine dehydrogenase (DPD) deficiency is an uncommon genetic condition that can result in severe toxicity from fluoropyrimidine chemotherapy. The authors conducted a model-based analysis to evaluate the cost-effectiveness of DPYD genotyping to screen for DPD deficiency; they found that screening led to improved quality-adjusted survival and was cost-effective.
- e196 **Induction Chemotherapy and Chemoradiotherapy Combined to ASA vs. Placebo for High-Risk Rectal Cancer: Results of a Randomized Trial**  
*Juliana Ominelli, Rodrigo O. de Castro Araujo, Marcus Valadão, Monica L.A. Padoan, Victor M. Lopes dos Santos, Jamille G. Dutra, Claudia C. Torres, Monique A. Barbosa, Raquel Guimarães, Juliana C. Carneiro Carvalho, Maria A. Ferreira, Ivanir M. de Oliveira, Isabele Small, Andréia C. de Melo, Luiz H. Araujo*  
 The ICAR trial aimed to evaluate induction chemotherapy followed by chemoradiotherapy with or without ASA on MRI tumor response. This single-center, double-blind, randomized phase II trial evaluated induction treatment with CAPOX, followed by capecitabine-based chemoradiotherapy with ASA (arm 1) or placebo (arm 2) in 27 patients. ASA during chemoradiotherapy was safe but failed to improve MRI tumor response.
- e205 **laparoscopic Colectomy: A Risk Factor for Postoperative Peritoneal Metastasis**  
*Hiroshi Nagata, Kazushige Kawai, Koji Oba, Hiroaki Nozawa, Shinichi Yamauchi, Kenichi Sugihara, Soichiro Ishihara*  
 This multicenter database study, including 17,323 patients with stage III colon cancer, revealed that the risk of postoperative peritoneal metastasis was significantly higher after laparoscopic colectomy than after open colectomy, especially in patients with pT4a colon cancer.
- e213 **Prognostic Role of Low-Skeletal Muscle Mass on Staging Computed Tomography in Metastasized Colorectal Cancer: A Systematic Review and Meta-Analysis**  
*Hans-Jonas Meyer, Alexandra Strobel, Andreas Wienke, Alexey Surov*  
 We evaluated the effect on low-skeletal muscle mass on overall survival in patients with metastasized colorectal cancer. We could show that LSMM is frequent in patients with colorectal cancer and is associated with overall survival in the first-line chemotherapy setting.
- e226 **Cure Rates According to Dose-Intensity of Chemoradiation in T2N0 Squamous Cell Carcinoma of the Anal Canal**  
*Iara K.F. Lustosa, Marcos P.G. Camandaroba, Bruna R.S. Mattos, Silmara F. Silva, Soledad Iseas, Rachel P. Riechelmann*  
 Patients with T2N0 squamous cell carcinoma of the anus experience improved complete clinical response and inferior colostomy rates when treated with standard chemoradiation in comparison to less intensive treatments.