



Illustration by Erin Moore

CLINICAL Colorectal Cancer

and Other Gastrointestinal
Malignancies

Volume 18, Number 2 • June 2019

Table of Contents

Review

- 81 **Biologics, Immunotherapy, and Future Directions in the Treatment of Advanced Cholangiocarcinoma**
Anwaar Saeed, Robin Park, Mohammed AlJumayli, Raed Al-Rajabi, Weijing Sun

Original Studies

- 91 **A Genomic Analysis Workflow for Colorectal Cancer Precision Oncology**
Giorgio Corti, Alice Bartolini, Giovanni Crisafulli, Luca Novara, Giuseppe Rospo, Monica Montone, Carola Negrino, Benedetta Mussolin, Michela Buscarino, Claudio Isella, Ludovic Barault, Giulia Siravegna, Salvatore Siena, Silvia Marsoni, Federica Di Nicolantonio, Enzo Medico, Alberto Bardelli
Accurate diagnosis and precision medicine of colorectal cancer (CRC) rely on patient-specific genomic maps. We present IDEA, an integrated DNA next generation sequencing and bioinformatic approach to determine the molecular landscape of CRC. First, genomic targets are predefined to obtain optimal sensitivity for tissue or blood samples. IDEA then pinpoints genetic variations with predictive and prognostic value, defines actionable targets, and unveils drug resistance mechanisms in patients with metastatic CRC. Results are presented in a final report, which includes clinically relevant information.
- 102 **Tumor Heterogeneity as a Predictor of Response to Neoadjuvant Chemotherapy in Locally Advanced Rectal Cancer**
Alissa Greenbaum, David R. Martin, Thérèse Bocklage, Ji-Hyun Lee, Scott A. Ness, Ashwani Rajput
A standard therapy for locally advanced cancers includes neoadjuvant chemoradiation; however, currently there is no way of knowing which patients have disease that will respond to such therapy. We analyzed 21 pretreatment rectal cancer biopsy samples and found a positive correlation of the response to therapy with a quantitative mutant-allele tumor heterogeneity (MATH) score. This next-generation sequencing derived score may serve as a biomarker for response to therapy.
- 110 **Impact of Sex on Chemotherapy Toxicity and Efficacy Among Patients With Metastatic Colorectal Cancer: Pooled Analysis of 5 Randomized Trials**
Omar Abdel-Rahman
This pooled analysis from 5 clinical trials of metastatic colorectal cancer patients found no difference in overall or progression-free survival between female and male subjects. Female subjects had a higher rate of gastrointestinal and hematologic toxicities.

- 116 Lack of Benefit From Anti-EGFR Treatment in RAS and BRAF Wild-type Metastatic Colorectal Cancer With Mucinous Histology or Mucinous Component**
Roberto Moretto, Federica Morano, Elena Ongaro, Daniele Rossini, Filippo Pietrantonio, Mariaelena Casagrande, Carlotta Antoniotti, Salvatore Corallo, Federica Marmorino, Francesco Cortiula, Federico Nichetti, Beatrice Borelli, Gemma Zucchelli, Alessandra Boccaccino, Gianluca Masi, Filippo de Braud, Alfredo Falcone, Chiara Cremolini
Adenocarcinoma with mucinous histology or mucinous component are histologic subtypes of metastatic colorectal cancers (mCRCs) with limited benefit from cytotoxic agents. Their sensitivity to anti-epithelial growth factor receptors (EGFRs) is not clear. We retrospectively identified patients with RAS/BRAF wild-type mCRC treated with anti-EGFRs. Our findings suggest no benefit from anti-EGFRs in mCRC with mucinous histology or mucinous component, irrespective of sidedness.
- 125 Phase II Study of Tivantinib and Cetuximab in Patients With KRAS Wild-type Metastatic Colorectal Cancer With Acquired Resistance to EGFR Inhibitors and Emergence of MET Overexpression: Lesson Learned for Future Trials With EGFR/MET Dual Inhibition**
Lorenza Rimassa, Silvia Bozzarelli, Filippo Pietrantonio, Stefano Cordio, Sara Lonardi, Laura Toppo, Alberto Zaniboni, Roberto Bordonaro, Maria Di Bartolomeo, Gianluca Tomasello, Vincenzo Dadduzio, Maria Chiara Tronconi, Chiara Piombo, Laura Giordano, Annunziata Gloghini, Luca Di Tommaso, Armando Santoro
There is a major need for therapeutic strategies able to overcome resistance to available treatments for patients with metastatic colorectal cancer. In this phase II study, we evaluated the combination of tivantinib and cetuximab in 41 molecularly selected patients with acquired resistance to anti-epidermal growth factor receptors and MET overexpression. Overall, our results suggest that this combination is not worth of further development.
- 133 FOLFOX and FOLFIRI Use in Stage IV Colon Cancer: Analysis of SEER-Medicare Data**
Alfred I. Neugut, Aijing Lin, Gabriel T. Raab, Grace Clarke Hillyer, Deborah Keller, Daniel S. O'Neil, Melissa Kate Accordini, Ravi P. Kiran, Jason Wright, Dawn L. Hershman
An examination of the demographic and clinical characteristics associated with the use of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRI) in patients with stage IV colon cancer found that FOLFOX is prescribed much more frequently than FOLFIRI as first-line therapy, especially in those who were female and those with fewer comorbidities. FOLFOX use has been increasing recently.
- 141 Right or Left Primary Site of Colorectal Cancer: Outcomes From the Molecular Analysis of the AGITG MAX Trial**
Gonzalo Tapia Rico, Timothy Price, Niall Tebbutt, Jennifer Hardingham, Chee Lee, Luke Buizen, Kate Wilson, Val GebSKI, Amanda Townsend
For metastatic colorectal cancer, previous reports have described differences in biology and outcomes, including response to biological therapies, based on the sidedness (left vs. right) of the primary lesion. We explored the molecular markers from the AGITG MAX trial and found that right-sided cancer patients had poorer outcomes. We also found that the effectiveness of bevacizumab was independent of the site of the primary lesion.
- 149 Colon Cancer Tumor Location Defined by Gene Expression May Disagree With Anatomic Tumor Location**
Emily Cannon, Steven Buechler
Tumor location is increasingly considered in designing treatment of colon tumors. In a microarray dataset (n = 871), we showed that tumor locations predicted by gene expression may disagree with anatomic locations, and were superior to anatomic locations in specifying key molecular features of the tumors. Mesenchymal tumors (CMS4) were likely to have ambiguous location as predicted by gene expression.

159 **Regorafenib Is Associated With Increased Skeletal Muscle Loss Compared to TAS-102 in Metastatic Colorectal Cancer**

Florian Huemer, Verena Schlintl, Stefan Hecht, Hubert Hackl, Thomas Melchardt, Gabriel Rinnerthaler, Richard Greil, Lukas Weiss

Regorafenib and TAS-102 therapy sequencing in metastatic colorectal cancer (mCRC) is still under debate. In a study of 32 mCRC patients, treatment with regorafenib was associated with a statistically significant skeletal muscle loss, which was not the case with TAS-102. Regorafenib should be used with caution in mCRC patients with preexisting sarcopenia or a history of recent weight loss.

**Available Exclusively Online at
www.clinical-colorectal-cancer.com**

e171 **Poorer Oncologic Outcome of Good Responders to PCRT With Remnant Lymph Nodes Defies the Oncologic Paradox in Patients With Rectal Cancer**

Eunhae Cho, In Ja Park, Seung Mo Hong, Jong Lyul Lee, Chan Wook Kim, Yong Sik Yoon, Seok-Byung Lim, Chang Sik Yu, Jin Cheon Kim

Prognostic impact of metastatic lymph nodes should be carefully considered in deciding treatment plan after preoperative chemoradiotherapy (PCRT). The decision to withhold patients from complete local control by total mesorectal excision after PCRT needs to be made with caution: nodal positivity, not readily detectable with tools currently used in clinical staging, could be more lethal than it was previously believed in patients with rectal cancer that have not undergone PCRT.

e179 **Metronomic Capecitabine With Cyclophosphamide Regimen in Unresectable or Relapsed Pseudomyxoma Peritonei**

Alessandra Raimondi, Salvatore Corallo, Monica Niger, Maria Antista, Giovanni Randon, Federica Morano, Massimo Milione, Shigeki Kusamura, Dario Baratti, Marcello Guaglio, Chiara Cremolini, Federica Marmorino, Maria Di Bartolomeo, Marcello Deraco, Filippo De Braud, Filippo Pietrantonio

No standard treatment for unresectable or recurrent pseudomyxoma peritonei has been defined. Our study showed that metronomic capecitabine with cyclophosphamide is a well tolerated and potentially active regimen in this disease setting. Neutrophil to lymphocyte ratio baseline < 3 , compared with ≥ 3 , showed a significant association with a prolonged progression-free survival.

e191 **Effect of Responsiveness of Lymph Nodes to Preoperative Chemoradiotherapy in Patients With Rectal Cancer on Prognosis After Radical Resection**

Hyun Gu Lee, Sung Joo Kim, In Ja Park, Seung Mo Hong, Seok-Byung Lim, Jung Bok Lee, Chang Sik Yu, Jin Cheon Kim

Metastatic lymph node status after preoperative chemoradiotherapy can be evaluated using the lymph node regression grade (LRG). In this study, the LRG was shown to discriminate prognostic groups, even within the same ypN stage, indicating that LRG can be considered a prognostic determinant in rectal cancer patients with metastatic lymph nodes after preoperative chemoradiotherapy.

e200 **A Review on the Scope of Photothermal Therapy–Based Nanomedicines in Preclinical Models of Colorectal Cancer**

M. Ibrahim Khot, Helen Andrew, Hafdis S. Svavarsdottir, Gemma Armstrong, Aaron J. Quyn, David G. Jayne

e210 **Network Mapping of Molecular Biomarkers Influencing Radiation Response in Rectal Cancer**

Liam Poynter, Dieter Galea, Kirill Veselkov, Alexander Mirnezami, James Kinross, Jeremy Nicholson, Zoltán Takáts, Ara Darzi, Reza Mirnezami

e223 **Pattern, Stage, and Time of Recurrent Colorectal Cancer After Curative Surgery**

Salman Yousuf Guraya

- e229 Updated Survival Analysis of the Randomized Phase III Trial of S-1 Versus Capecitabine in the First-Line Treatment of Metastatic Colorectal Cancer by the Dutch Colorectal Cancer Group**
Johannes J.M. Kwakman, Erik van Werkhoven, Lieke H.J. Simkens, Johan M. van Rooijen, Yes A.J. van de Wouw, Albert J. ten Tije, Geertjan M. Creemers, Mathijs P. Hendriks, Maartje Los, Robbert J. van Alphen, Marco B. Polée, Erik W. Muller, Ankie M.T. van der Velden, Theo van Voorthuizen, Miriam Koopman, Linda Mol, Cornelis J.A. Punt
- e231 Disqualification of Neoadjuvant Rectal Score Based on Data of 6596 Patients From the Netherlands Cancer Registry**
Maxime J.M. van der Valk, Floris A. Vuijk, Hein Putter, Cornelis J.H. van de Velde, Geerard L. Beets, Denise E. Hilling
 We aimed to validate the neoadjuvant rectal score (NAR) using data of 6596 patients from the Netherlands Cancer Registry. We found that the prognostic value of the NAR score was inferior to a simple regression model with the factors clinical tumor stage, pathologic tumor, and nodal stage. Therefore, we advise against using the NAR score as a surrogate endpoint.
- e237 Survival Outcomes After Surgical Management of the Primary Tumor With and Without Radiotherapy for Metastatic Rectal Adenocarcinoma: A National Cancer Database (NCDB) Analysis**
Paul Renz, Rodney E. Wegner, Shaakir Hasan, Robert Brookover, Gene Finley, Dulabh Monga, Moses Raj, James McCormick, Alexander Kirichenko
 The present study examines outcomes in patients with stage IV rectal cancer receiving some form of local therapy. That local therapy was either surgery alone or chemoradiation followed by surgery. The authors' analysis showed a benefit to the addition of chemoradiation to surgery, even in the metastatic setting highlighting the need for multidisciplinary management in this patient population.
- e244 Tumor-associated Macrophages and Neuroendocrine Differentiation Decrease the Efficacy of Bevacizumab Plus Chemotherapy in Patients With Advanced Colorectal Cancer**
Fatma Sena Dost Gunay, Bilge Ayca Kirmizi, Arzu Ensari, Fikri İcli, Hakan Akbulut
 No predictive marker is available for antiangiogenic treatment modalities in routine practice. The present study included a group of patients with advanced colorectal cancer, including 123 consecutive patients treated with bevacizumab plus chemotherapy, to determine the predictive and prognostic role of tumor-associated macrophages (TAMs) and neuroendocrine differentiation (NED) of primary tumor tissue. High TAM infiltration and the presence of NED in tumor tissue were predictors for poor survival.
- e251 Neuroendocrine Differentiation, Microsatellite Instability, and Tumor-infiltrating Lymphocytes in Advanced Colorectal Cancer With BRAF Mutation**
Nunzio Digiaco, Elena Bolzacchini, Giovanni Veronesi, Roberta Cerutti, Nora Sahnane, Graziella Pinotti, Marco Bregni, Salvatore Artale, Claudio Verusio, Filippo Crivelli, Carlo Capella, Fausto Sessa, Daniela Furlan
 A clinicopathologic analysis of 59 cases of advanced colorectal cancer with BRAF mutation was performed to compare microsatellite unstable and stable cases, focusing on the inflammatory profiles and neuroendocrine differentiation of these tumors. Microsatellite stable tumors showed a high frequency of neuroendocrine differentiation. The combined presence of microsatellite instability and high CD8 T-cell content was associated with a 63% reduction in the risk of death.
- e261 Trends in Colorectal Cancer Incidence and Survival in Iowa SEER Data: The Timing of It All**
Rachel Carroll, Shanshan Zhao
 Colorectal cancer is common worldwide. Our results indicated that both overall and older onset colorectal cancer incidence began to decline in the early 2000s, whereas younger onset incidences decreased until the late 1980s but then increased steeply through the 2000s. These and other results suggested that regular colorectal screenings could reduce incidence and mortality in people under 50.