Colorectal cancer is the second main cause of cancer-related death in the Western world. Currently, approximately 75% of patients with colorectal cancer present with locally advanced disease; however, despite curative surgery, around 40% of patients will still experience disease relapse leading to morbidity and eventual mortality. In the postoperative setting, there is now clear evidence that adjuvant chemotherapy significantly improves clinical outcomes in patients with colorectal cancer. Chemotherapeutic drugs such as fluoropyrimidines and oxaliplatin are now used as part of standard care, and the arsenal of new therapies with significant activity in this disease is steadily growing. Nonetheless, the management of patients with potentially curative, locally advanced stage II and III disease remains an active area of clinical debate as the overall combined 5-year survival for these patients is approximately 65%. Indeed, only one third of the 40% of patients who are at risk of relapse derive any significant benefit from adjuvant chemotherapy treatment. Moreover, in the metastatic disease setting, combinations of fluorouracil with agents such as irinotecan and oxaliplatin plus novel targeted agents such as antivascular endothelial growth factor inhibitors, like bevacizumab (Avastin®; Genentech, South San Francisco, CA), and epidermal growth factor receptor inhibitors, such as cetuximab and panitumumab, have also led to significantly improved response rates of approximately 45%–50% and improvements in survival in patients with metastatic disease. Therefore, the therapeutic repertoire for patients with colorectal cancer has now expanded to a point where there are many more choices in terms of treatment, clinical trial design, and greater therapeutic impact than ever before. In addition to these therapeutic advances, there have been a number of other important advances over the past decade, such as genomic, proteomic, and imaging technologies that have begun to have significant implications for both clinical and basic research in colorectal cancer as well as patient management. Advances in technology such as gene expression microarrays, high throughput sequencing, and molecular and functional imaging approaches have begun to facilitate the integration of tumor biology and functional data in patient treatment, allowing a better understanding of how the biology of the disease may impact clinical decision making. Nonetheless, for most therapeutic agents, it is still not currently possible to identify those patients most likely to benefit on the basis of their genetic profile nor is it possible to identify those patients who are likely to experience adverse side effects. Clearly, the identification and understanding of these biological factors has the potential to allow oncologists and the drug development process to appropriately select therapeutic agents while adjusting the dose and combination regimen to allow more successful outcomes and avoid significant toxicity and morbidity.

In an attempt to address some of these issues, an international Colorectal Cancer Coalition (CCC) was formed to provide an interactive, integrated, and effective international forum in which to openly address these major challenges now facing the colorectal cancer community. The papers presented in this edition of The Oncologist represent a summary of the key presentations and discussions that took place during the inaugural convocation of the CCC. Although concentrating primarily on the impact of novel and recent advances in the treatment of colorectal cancer, as well as the impact of novel targeted therapies and new technologies, participants engaged in in-depth discussion and challenging debate that both identified
problems and suggested important solutions to those issues that prevent us from easily translating the power of new technology and cellular biology to ultimate patient benefit.

The papers that follow address some of the major clinical issues facing the colorectal community today.

**Dr. Benson** [1] highlights the data from patients for both stage II and stage III locally advanced disease within the postoperative adjuvant setting. His paper highlights the fact that in stage III patients, the benefit of adjuvant therapy is now well documented, and the extent of this benefit relates to tumor grade invasion and nodal involvement. By contrast, his paper goes on to give a very good overview of the arguments for and against adjuvant therapy for patients in stage II disease, where 25% of patients will have disease recurrence despite surgery and adjuvant chemotherapy and, at most, adjuvant chemotherapy will benefit only 3%–4% of patients treated. This review also highlights the importance of future studies’ incorporating molecular markers in the design of adjuvant trials.

**Dr. Goldberg’s** critical review [2] summarizes the impact of novel therapies in combination with chemotherapy on the median overall survival of patients presenting with metastatic colorectal cancer. Patients receiving first- and second-line combination chemotherapy now can expect to live more than 20 months, and (particularly in those studies incorporating oxaliplatin) patients may now potentially have curative resection of advanced disease, which would have been previously impossible. This paper also points to the challenges that currently face the optimal treatment of metastatic colorectal cancer, addressing issues such as optimum sequencing of chemotherapy and combinations of chemotherapy and biological targeted agents.

**Dr. Schmoll and Dr. Arnold** [3] present an important new development in colorectal cancer treatment using oral 5-fluorouracil (5-FU) in the form of capecitabine. Their paper focuses on the oral 5-FU analogue capecitabine and suggests that oral agents such as capecitabine may ultimately replace 5-FU, both as a single-agent therapy and also in combinations with agents such as oxaliplatin, irinotecan, and indeed novel targeted therapies such as bevacizumab and cetuximab. Moreover, they also examine the use of preoperative capecitabine in combination with radiotherapy and its preliminary exciting results in relation to complete response in rectal cancer. Nonetheless, while capecitabine would appear to be generally well tolerated, their paper points to the importance of noting the potential toxicities that need careful management, especially in combination regimens.

A very interesting paper presented by **Dr. Ryan** [4] examines the role of nonsurgical approaches to the treatment of metastatic colorectal cancer. He carefully challenges the current orthodoxy (to use his words) that governs both surgical and nonsurgical methods of tumor reduction such as chemoembolization and radiofrequency ablation. He suggests that we develop a more comprehensive phase III clinical trial program that evaluates these methodologies rather than relegating them to the clinical trial dustbin.

Other papers examine the challenges that we face in applying the armamentarium of novel targeted agents in the treatment of colorectal cancer. **Dr. Van Cutsem** [5] examines the challenges in the use of existing epidermal growth factor–targeted agents such as cetuximab and panitumumab and their roles in both first- and second-line treatment of metastatic disease. This paper also addresses the management of toxicities, particularly skin rash, and addresses the issue of how to appropriately select patients for EGFR-targeted therapies. **Dr. O’Dwyer** [6] addresses the issues surrounding the addition of antiangiogenic agents, such as bevacizumab, to chemotherapy and speculates on their mechanism of action and how they may best be integrated with established treatment going forward. **Dr. Wilson** [7] examines other novel therapeutic developments such as liposomal thymidylate synthase inhibitors; the multi-targeted antifolate MTA and thymectacin; a novel topoisomerase 1 inhibitor, edotecarin; and the PARP (poly[ADP-ribose] polymerase) inhibitor, AGO41699. He also points to the wealth of other novel targeted agents being investigated in colorectal cancer and highlights the fact that the pipeline for novel drugs for colorectal cancer is very encouraging and likely to yield even further advances in the near future. Finally, the paper by **Dr. Harkin** [8] looks at the impact of new genomic technologies in both the preclinical and clinical drug development process in colorectal cancer. He discusses the impact of gene expression microarrays and their use in preclinical and clinical drug development and their likely impact on colorectal cancer. He highlights the fact that these technologies can now identify novel targets and select patients most likely to benefit from molecules designed to target these. This review also highlights how these technologies can both speed drug development and, more appropriately, define those patients who truly benefit from them.

All of these papers represent a summation of the discussions and debate that took place during the inaugural CCC meeting. They exemplify the need for a forum such as CCC whereby international leaders have the opportunity to ponder the future of clinical development in a disease such as colorectal cancer. Moreover, the papers highlight important developments that have happened very quickly.
in both metastatic and locally advanced colorectal cancer disease and challenge our ability to meaningfully exploit our understanding of tumor biology and modern technology. If we are to achieve the Holy Grail of molecularly driven studies in colorectal cancer that incorporates biology, functional imaging, and novel clinical design, then the next generation of clinical studies will have to be designed in an integrated manner that allows the incorporation of cell biology and novel technologies alongside the clinical development process.

**Disclosure of Potential Conflicts of Interest**

P.G.J. has acted as a consultant for Amgen.

**References**