

# Translational Research in Colorectal Cancer

## Taormina, Italy

### 25 October 2008

Few research breakthroughs in preclinical science have translated into meaningful benefits—in clinical terms or quality of life—for colorectal cancer patients. Seeking ways to span the gap between preclinical discovery and patient benefit was the focus of a meeting on Translational Research on Colorectal Cancer, 25 October 2008, attended by leading scientists and physicians.

Most translational research occurs in the context of industry-sponsored clinical trials. Industry has been slow, however, to investigate and utilize biomarkers, which can be used not only to select patients and monitor treatment, but also to develop new targeted therapies. Academic researchers thus have an opportunity to carry out independent research that can lead to biomarker discovery.

EACR sponsored this meeting jointly with the Biotherapy Development Association (BDA; [www.bdaoncology.org](http://www.bdaoncology.org)). Heinz Zwierzina of the Innsbruck Medical University introduced BDA as an international organisation devoted to education, preclinical and clinical research, and development of biological therapies for cancer. BDA delegates represent the pharmaceutical industry, academia, regulatory agencies, and patient advocacy groups in the EU, the United States, China, Japan, and elsewhere.

The meeting became a novel and exciting brain-storming session with two important goals: (1) garner input from renowned academic investigators who understand what's needed from early phase clinical research to make breakthroughs in colorectal cancer; and (2) provide opportunity for preclinical scientists to better understand translational research from clinical scientists' point of view.

Key opinion leaders in the academic world shared their ideas about directing preclinical research toward early diagnosis and more effective colorectal cancer treatment. The participants presented research findings, discussed areas for future translational studies, and identified needed resources. A position paper based on the meeting proceedings is being prepared for journal submission.

Discussions centred on biomarkers (e.g., *KRAS*) for defining subgroups of patients who are more likely to respond to a molecularly targeted therapy and the need for using more complex tools (e.g., proteomics, epigenetics), findings from clinical trials of monoclonal antibodies used as monotherapy or in combination with chemotherapy, clinical trial designs that incorporate biomarker-based patient selection and monitoring, and the compelling need for access to biopsy specimens for *ex vivo* studies.

A growing body of evidence implicates *KRAS* in colorectal cancer development and points to its potential importance as a predictive and prognostic biomarker and as a target for therapy. Manuela Gariboldi (Istituto Nazionale dei Tumori, Milan, Italy) spoke about multidimensional molecular characterization of colon cancer. Her group has focused on identifying mutations and gene expression alterations, downstream from the epidermal growth factor receptor (EGFR), and implicated in colorectal cancer. These are mainly found in samples with an increased *EGFR* copy number. Among 25 *EGFR*-amplified cases, they found a high frequency of mutated *KRAS* (60%), alterations in the AKT/mTOR pathway (36%), and loss of PTEN (24%).

In his presentation, Fortunato Ciardiello of the Second University of Naples also emphasised the significance of *KRAS* mutations and noted that their activation is an early event in colorectal carcinogenesis. Such mutations can be detected very early, even in aberrant crypt foci. About 40% of colorectal cancer patients have *KRAS* mutations, which may be associated with a poor prognosis. Recent data show that cetuximab, an anti-EGFR monoclonal antibody, is more efficacious as first-line therapy in colorectal cancer patients with wild-type *KRAS* tumours, underscoring this gene's role in the disease and its treatment.

According to Eric Van Cutsem of the University Hospitals Leuven, data from several studies have shown that cetuximab and panitumumab were more efficacious in refractory colorectal cancer patients with wild-type *KRAS*. The phase III CRYSTAL trial retrospectively investigated the effect of *KRAS* mutation status on first-line treatment of metastatic colorectal cancer with FOLFIRI, with or without cetuximab, and showed that overall survival was significantly prolonged in patients with wild-type *KRAS* regardless of the therapy. Those treated with the combination therapy had the greatest benefit in overall survival. Eric pointed out that *KRAS*, therefore, is the first biomarker used to select a targeted therapy in combination with a standard chemotherapy regimen.

Salvatore Siena (Ospedale Niguarda Ca' Granda, Milan) reviewed several clinical trials of panitumumab used as monotherapy or combined with conventional chemotherapy. Initially, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion of panitumumab for metastatic colorectal cancer, but subsequent data have shown that patients with non-mutated *KRAS* received clinical benefit. Consequently, CHMP granted a conditional marketing authorisation for the drug in this setting. Salvatore also presented findings that patients treated with panitumumab who had wild-type *KRAS* reported better quality of life than those with mutated *KRAS*.

Alberto Bardelli of the University of Torino (Candiolo, Italy) spoke about the significance of mutations in the EGFR-signalling cascade and the use of new, cell-based pharmacogenomic studies to predict response to targeted therapies. By comparing parent and knock-in cell lines, his group is screening more than 130 compounds to learn which are more effective in either wild-type or mutant *KRAS*, *BRAF*, *PIK3CA*, and *EGFR* genotypes.

Anti-angiogenesis is also a viable target in colorectal cancer. Diether Lambrechts (Vesalius Research Center, Leuven) commented on the genetics, epigenetics, and pharmacogenetics of this mechanism, emphasising vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab. Some tumours do not respond well to bevacizumab and others eventually revascularize. Hans Schmoll (Martin-Luther-University, Halle, Germany), has also studied bevacizumab and found that up to 30% respond to VEGF, at least initially, and that VEGF inhibitors have effects against other tumour types (e.g., lung). D. Lambrechts investigations have focused on mechanisms of resistance to angiogenesis inhibitors, specifically angiogenic factors that revascularize a tumour, genetic determination, oncogenic mutations, and methylation. He advanced ideas about designing trials to explore these factors and underscored the importance of obtaining serial plasma, DNA, and tumour samples.

Beyond VEGF and *KRAS*, other biomarkers will be needed for understanding colorectal cancer and developing new treatments. Proteomics—the study of proteins, their posttranscriptional modification, when and where they are expressed, and their interactions in metabolic pathways and with one another—was Heinz Zwierzina's subject. As of October 2008, more than 3,500 articles had been published on cancer proteomics. Despite the revolution in disease detection and tailored therapies, more work is needed to identify the

most suitable techniques and samples, elucidate whether proteins are causative or 'bystanders', and clinically validate proteomic markers.

Epigenetic biomarkers also show promise. Guro Lind (Norwegian Radium Hospital, Oslo) pointed out that colorectal cancer's slow course provides a window of opportunity for very early diagnosis. Her group is developing noninvasive screening based on DNA promoter methylation of five target genes. Combining biomarkers in this way ensures high sensitivity and specificity. Josep Tabernero (Vall d'Hebron University Hospital, Barcelona) offered reasons why new molecules that show promise in early development fail in phase III pivotal trials and described how biomarker development programs might ameliorate excessive attrition. Broader biomarker application will likely expedite drug development and boost overall success rates, but biomarker studies require biopsy specimens. An ideal clinical trial of molecularly targeted agents would collect biopsies and analyse them genomically/proteomically at the outset (for patient selection), during (to monitor treatment effects), and at disease progression (to select or add a new therapy).

Nevertheless, significant regulatory and institutional barriers exist to collecting and sharing biopsy tissue. Participants agreed that biopsy specimen access is the key to achieving personalised medicine because specimens provide genetic and molecular information about patients' tumours that can be exploited by molecularly targeted anticancer therapies.



**Greek amphitheatre in Taormina**