

Measured Progress Observed in Colorectal Cancer Therapy



Debu Tripathy, MD
Editor-in-Chief

It seems that the progress curve for every cancer type experiences an inflection (several over time) as new approaches are introduced – in some cases, long lulls intercede. The story for advanced colorectal cancer and what it means for today's practice is nicely outlined in this issue of AJHO by Dr. King and colleagues. For colorectal cancer, the tires were stuck in the mud for many years with fluorouracil (and other fluoropyrimidines in countries like Japan) as the only medical therapeutic class, and it was not even clear that this even improved outcomes in either early or advanced stages of disease. It was not until the testing of oxaliplatin and irinotecan that clear improvements were seen – and these were still modest. Shortly thereafter, the addition of biologics, notably bevacizumab and cetuximab, again produced outcome advantages. However, the luster of targeted therapy in the age of precision therapy was difficult to claim with the lack of biomarkers to personalize therapy or point the way to newer strategies. Almost simultaneously, several retrospective analyses, showed that *RAS* activating mutations predicted lack of response to cetuximab – prompting the unusual move by the FDA to include this information in the label. This provided some decision branch points for treatment, and in the last few years, trials attempting to define best biological option for *RAS* wild-type tumors yielded mixed results – one showing better results with cetuximab compared to bevacizumab and another not able to confirm those results.

What have we learned along that way that points to future opportunities? Another activating lesion in the *RAS-RAF-ERK* pathway is due to *BRAF* mutations, similar to those seen in melanoma, and as expected, these also predict resistance to EGFR-targeting therapy. But *BRAF* inhibitors are not active against colorectal cancers as they are for melanoma, probably due to more complex genomic aberration leading to more “rewiring” and bypass pathways. For this reason, rationally composed combinatorial regimens for this pathway are being explored. On the other hand, the phenotype of mismatch repair seen in a minority of colorectal cancer seems to make cancers more immunogenic, with more robust responses to immune checkpoint inhibitor therapy. Definitive immunotherapy trials are now underway for this subset. Other biological pathways involved colorectal cancer such as Wnt/ β -catenin signaling are amenable to targeting and showing some promising results in preclinical models, with clinical trials not too far behind. This review is in a sense a model essay of measured progress and portends yet another inflection for colorectal cancer therapy.

The American Journal of Hematology/Oncology is accepting manuscripts for immediate consideration.

Articles of interest include:

- Original research
- Reviews
- Emerging guidelines
- Case reports
- Pivotal trials

Please send manuscripts to Anthony Berberabe (aberberabe@mjhassoc.com).

EDITORIAL STAFF

Editor-in-Chief

Debu Tripathy, MD
Professor and Chair
Department of Breast Medical Oncology
The University of Texas
MD Anderson Cancer Center
Houston, TX

Associate Editor

Jason J. Luke, MD, FACP
Assistant Professor of Medicine
University of Chicago
Chicago, IL

Managing Editor

Tony Berberabe, MPH
aberberabe@mjhassoc.com

Art Director

Paul Tresten

Editorial Offices

Physicians' Education Resource®, LLC
666 Plainsboro Road, Ste 356
Plainsboro, NJ 08536
(609) 378-3701



President

Phil Talamo, CHCP

Medical Director

Michael Perlmutter, PharmD, MS



CORPORATE OFFICERS

Chairman and CEO

Michael J. Hennessy, Sr

Vice Chairman

Jack Lepping

President

Mike Hennessy, Jr

Chief Financial Officer

Neil Glasser, CPA/CFE

**Executive Vice President,
Oncology Professional Relations**
Donna Short

Chief Marketing Officer

Warren Dardine

Chief Digital Strategy Officer

Steve Ennen

**Vice President of Editorial Services
and Production**
Kerrie Keegan

Vice President, Digital Media

Jung Kim

Chief Creative Officer

Jeff Brown

Human Resource Director

Shari Lundenberg