**CRC in Focus**

**The Next Generation of Targeted Therapy Trials in Colorectal Cancer**

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**H&O** What targeted therapies are currently available for treating colorectal cancer?

**PJO** The targeted therapies that have been approved for use in colorectal cancer are bevacizumab (Avastin, Genentech), cetuximab (Erbitux, Bristol-Myers Squibb/Lilly), panitumumab (Vectibix, Amgen), ziv-aflibercept (Zaltrap, Sanofi/Regeneron), and regorafenib (Stivarga, Bayer).

Bevacizumab and ziv-aflibercept are both antiangiogenic drugs that target vascular endothelial growth factor (VEGF), although ziv-aflibercept targets VEGF in a way that is different than bevacizumab. Cetuximab and panitumumab target endothelial growth factor receptor (EGFR), and regorafenib—which is a small molecule derivative of sorafenib (Nexavar, Bayer/Onyx)—targets many kinases, including the VEGF receptor VEGFR2.

Lilly recently announced that the antibody agent ramucirumab (Cyramza, Lilly), which has been approved for use in for certain patients with advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma, has shown early positive results for colorectal cancer. This antiangiogenic agent differs from bevacizumab and aflibercept by targeting VEGFR2. We are eager to see the data from that particular molecule in 2015.

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**H&O** What are the limitations of currently available targeted treatments for colorectal cancer?

**PJO** The biggest limitation is that we do not have drugs that are active in and specific for the most common aberrations that are found in colorectal cancer. For example, although more than 60% of colorectal tumors are aberrant in either KRAS or TP53, these are targets for which we do not yet have specific drugs.

Another limitation is that antiangiogenesis agents are not working as well as we had hoped they would. Although targeting angiogenesis has been useful in metastatic colorectal cancer—bevacizumab increased overall survival by about 5 months in the initial trial by Hurwitz and colleagues in 2004—patients become resistant over time. Of even greater concern is the fact that antiangiogenic agents have been shown to be ineffective as adjuvant therapy for colorectal cancer. We know that the adjuvant setting is where tumor cells are most sensitive to chemotherapy, so the fact that antiangiogenesis agents are ineffective in this environment means that they are not adding to our ability to cure colorectal cancer.

The concerns are somewhat different with EGFR inhibitors. In contrast with angiogenesis inhibitors, which generally are pretty well tolerated—severe side effects are rare, and most patients experience virtually no side effects—patients taking EGFR inhibitors often experience bothersome skin-related effects. One of the side effects that patients tend to find quite distressing is an acneiform rash.

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**H&O** What other targeted agents are being studied for use in colorectal cancer?

**PJO** Many experimental agents are being studied for use in colorectal cancer—especially in molecularly defined subgroups. Agents are being studied that target tumors with KRAS mutations and those with aberrations in the phosphatidylinositol 3-kinase (PI3K) signaling pathway, which are frequent in colorectal cancer. Approximately 4% of patients with metastatic colorectal cancer have a muta-
tion in \textit{BRAF}, and these patients tend to fare substantially worse than those without the mutation—their disease is associated with lower levels of response to therapy and shorter survival. We know that RAF inhibitors are highly effective in melanoma, which is a disease in which \textit{BRAF} is much more commonly aberrant.

When we first began testing RAF inhibitors in colorectal cancer, it was not nearly as easy to identify patients with a mutation in \textit{BRAF} as it is now. In a study I participated in with Scott Kopetz as the principal investigator, which was presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2010, we found relatively little benefit from an oral inhibitor of the mutant BRAF kinase in a group of 19 previously treated patients with metastatic colorectal cancer who had \textit{BRAF} V600E mutations. In contrast, at the 2014 ASCO meeting, a group led by Johanna Bendell demonstrated a significant rate of response with a 3-drug combination of trametinib (Mekinist, GlaxoSmithKline), dabrafenib (Tafinlar, GlaxoSmithKline), and panitumumab (Vectibix, Amgen) in patients with \textit{BRAF} V600E-mutated colorectal cancer. Although these results are preliminary, they represent the first evidence of highly effective targeting of this pathway in a population of patients who typically do poorly. Since then, studies have opened in the National Cancer Institute’s cooperative groups to test multidrug approaches in this population. Demonstrating the ability to target this subgroup is an important proof of principle.

\textbf{H\&O Are all of the trials that are looking at targeted therapy for treatment of colorectal cancer incorporating biomarker testing?}

\textbf{PJO} Unfortunately, the answer is no because the nature of targeted therapy varies. For example, we can target angiogenesis but we do not have biomarkers to identify which patients are going to respond. That is the case with many of the targeted therapies that currently are available, such as proteasome inhibitors and inhibitors of autophagy. Of course, we would prefer that all of the drugs we test have a biomarker, but that is not always the case. Sometimes the science has to catch up with the therapeutics.

\textbf{H\&O What is the most appropriate trial design to assess the activity of a single targeted agent or combination of agents in a molecularly defined subpopulation?}

\textbf{PJO} The answer to that question depends on several factors. First, it depends on the amount of preliminary data one has for the targeted agent and for the combination. We often confront this in designing the ASSIGN trial. Second, it depends on the frequency of the molecular subgroups we are dealing with. For example, approximately 1% of patients with colorectal cancer have an \textit{ALK} mutation. How do we get data on a variation that affects just 1% of the population? One way is to do the study and test the ALK inhibitor in that setting, so the design of that study would be single-arm phase 2. You would treat a certain number of patients in the phase 2 trial and determine whether there is a level of activity that is worthy of pursuing further.
By the same token, you would not proceed with a study on an agent for patients with RAS wild-type colorectal cancer unless you had preliminary data to suggest that the agent would be effective in these patients. Approximately 35% of patients with colorectal cancer are RAS wild-type.

Third, a registration strategy is borne in mind for each molecular subgroup with the hope that, should activity be demonstrated, a definitive impact of the drug sufficient for US Food and Drug Administration (FDA) approval could be defined. A phase 2/3 design can accelerate development for this purpose. If we have reason to believe that an effective targeted therapy might be superior to chemotherapy in that setting, a targeted therapy vs chemotherapy trial is most appropriate. The FDA likes to see studies with this design because it isolates the targeted therapy and compares it with a treatment already approved for the indication. Alternatively, some targeted therapies may work better with chemotherapy; for these, a design of chemotherapy plus the targeted therapy is appropriate.

**H&O** Do you see targeted therapy being used someday without conventional chemotherapy?

**PJO** Ultimately, yes. But in the meantime, chemotherapy remains important. We know that chemotherapy works in a large proportion of patients with colorectal cancer; it can be curative for patients with stage 3 disease when used in the adjuvant setting. That is why we need to try to identify the characteristics of patients who respond to chemotherapy, and those that might predict response to particular chemotherapeutic agents.

We also should try to understand, using other molecular approaches, what the characteristics are that make particular patients more or less resistant to chemotherapy. The goal would be to modify that resistance, making chemotherapy more effective. I think that before replacing chemotherapy with targeted therapy, we will see chemotherapy relegated to a secondary role.

**Suggested Readings**

Bendell JC, Atreya CE, André T, et al. Efficacy and tolerability in an open-label phase I/II study of MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in combination in patients (pts) with BRAF V600E mutated colorectal cancer (CRC) [ASCO abstract 3515]. *J Clin Oncol*. 2014;32(5)(suppl).


