

# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

## The Use of Genetic Alterations in the Development of Liver Cancer Drugs



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### G&H In which types of cancer can genetic alterations guide therapy?

**GAA** Genetic alterations—and, more specifically, somatic alterations—within a tumor help guide therapy in a variety of solid tumors, including lung cancer and colorectal cancer, but not yet primary liver cancer or hepatocellular carcinoma (HCC). The use of genetic alterations in the latter set of tumors remains in the research stage, with the ultimate goal being the use of mutational analysis to prescribe custom-made therapy rather than one-size-fits-all therapy.

### G&H Which signaling pathways are targeted in existing HCC treatment?

**GAA** The only agent that has been approved by the US Food and Drug Administration and globally for use in HCC is sorafenib (Nexavar, Bayer/Onyx), which is a multikinase inhibitor that includes the vascular endothelial growth factor as a target. SHARP (Sorafenib HCC Assessment Randomized Protocol Trial), a phase 3 study of 602 patients with unresectable HCC, found that overall survival was significantly longer in patients randomly assigned to sorafenib (10.7 months) than to placebo (7.9 months). The positive outcome study that helped establish the standard of care for the treatment of advanced HCC led to the development of interest in evaluating other, even more selective antiangiogenics in the same settings. However, none of these studies yielded any survival advantage beyond what sorafenib provides. These studies

confirm the fact that HCC seems to be a multitarget disease, and so far there has been no single pathway that is known to be critical. The virtues of sorafenib may thus lie in its multitargeted nature.

As such, the interest in the angiogenic pathway for HCC has started to wane, although there is still one phase 3 trial of the antiangiogenic drug lenvatinib (Lenvima, Eisai), the results of which have yet to be reported. This study is randomly assigning patients with unresectable HCC to first-line treatment with lenvatinib or sorafenib (NCT01761266).

The different etiologies that lead to HCC, and the different genetic alterations that they may cause, could suggest differing pathways to address. However, there is no scientific evidence or prospectively conducted study to prove such a theory. Some retrospective work, nonetheless, has suggested an improved overall survival outcome from sorafenib in patients with HCC who also have hepatitis C virus infection. This can be attributed to the overexpression of RAF—one of the sorafenib targets—in patients with hepatitis C virus infection. Of course, these retrospective findings do not invalidate the value of sorafenib for patients with hepatitis B virus infection.

### G&H Which signaling pathways are the focus of current studies of HCC treatment?

**GAA** The other pathway that has earned quite a bit of attention is the MET pathway. c-MET is the receptor for hepatocyte growth factor. At least two phase 3 clinical trials are focusing on the c-MET pathway in HCC.

One of these studies is examining cabozantinib (Cometriq, Exelixis; NCT01908426), and the other one is examining the investigational agent tivantinib (NCT01755767). Both of these agents are inhibitors of multiple tyrosine kinases, including c-MET.

Regarding pathways, CELESTIAL (Study of Cabozantinib [XL184] Vs Placebo in Subjects With Hepatocellular Carcinoma Who Have Received Prior Sorafenib) examines the use of cabozantinib, which is administered to patients with advanced HCC regardless of their c-MET expression. The rationale for this approach is 2-fold: first, it remains unclear what level of c-MET expression represents positivity, and second, cabozantinib is a multikinase inhibitor.

In contrast, METIV-HCC (Study of Tivantinib in Subjects With Inoperable Hepatocellular Carcinoma Who Have Been Treated With One Prior Therapy) is only enrolling patients who are positive for high levels of c-MET expression, which is defined here as at least 50% of tumor cells with strong (3+ or 4+) staining intensity. This criterion is based on findings of a randomized phase 2 study of tivantinib vs placebo in the second line of HCC treatment, which suggested a negative prognostic value for high c-MET expression and an improved survival outcome among those patients when treated with tivantinib.

### **G&H** Which other signaling pathways are the focus of current studies of HCC treatment?

**GAA** Interest in immune modulation in HCC is at an all-time high right now. The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) pathways have already been suggested as key targets in HCC. We have already started to see intriguing data published on checkpoint inhibitors for HCC. The anti-CTLA-4 agent tremelimumab (formerly ticilimumab, CP-675,206; Pfizer) has already been tested as a single agent and in combination with local interventions. As a single agent, it achieved a partial response of 17.6% as well as a virologic response among patients with HCC and hepatitis C virus infection that was quite intriguing. Similarly encouraging results were reported with the use of the anti-PD-L1 agent durvalumab (MedImmune) and the anti-PD-1 agent nivolumab (Opdivo, Bristol-Myers Squibb), with the latter showing a response rate of 19%, including a complete response rate of 5%.

Several studies are expected right away that will investigate the role of the different immune modulators in advanced HCC, considering such global response rates. From the perspective of genetic changes, however, the role

that CTLA-4, PD-1, or PD-L1 expression may play in regard to outcome remains unknown.

### **G&H** Do all patients with HCC undergo tissue biomarker testing?

**GAA** Many institutions and several commercial entities are performing somatic mutational analysis on cancers using a battery of predefined genes of interest. At Memorial Sloan Kettering Cancer Center, patients with HCC and other cancers are offered the possibility of analyzing more than 400 genes, and recently germline mutational analysis has been offered.

Bearing in mind the heterogeneity of HCC, we are planning in another project to complete a mutational analysis of patients of different ethnicities who have HCC of different etiologies in order to perform a comparison. For example, patients with HCC who also have hepatitis B virus infection and are from Hong Kong are compared with patients with HCC who also have hepatitis C virus genotype 4 infection and are from Egypt. This project will provide a one-of-a-kind opportunity to examine any differences in the makeup and outcomes of HCC in different settings.

### **G&H** Are there any pitfalls that specialists need to be aware of regarding tumor markers in HCC?

**GAA** It is important to remember that HCC is a complex disease. It has different etiologies and behaves differently in various ethnicities. These facts may become important to the research being conducted, and it may not be surprising to one day see etiology- and/or ethnicity-specific HCC clinical trials.

Another factor that adds to the complexity of HCC is that it usually involves 2 diseases. Most patients with HCC have underlying liver cirrhosis, which might influence outcome, affect therapy, and impose certain limitations on clinical trials. These possibilities undermine the critical need for the multidisciplinary management of HCC.

### **G&H** Could tumor markers play a role in the surveillance of HCC?

**GAA** It would be very helpful if a panel of biomarkers could indicate if a patient is susceptible to HCC or has it already, but we are not there yet. Alpha-fetoprotein might serve that role, but there is continued debate about its validity, enough that certain academics advocate against its use and confine the surveillance of HCC to routine radiologic evaluation for patients at risk.

## G&H What are the next steps in research in this area?

**GAA** The focus for the next several years will be on immune modulation. However, a continued and evolving interest in etiology-based outcome is also expected.

*Dr Abou-Alfa has received research support from Amgen, Bayer, BMS, Exelixis, Genentech, MedImmune, Novartis, and Polaris Pharmaceuticals. He has also served as an advisor to BMS and MedImmune.*

### Suggested Reading

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