INTERVIEW

Bert H O'Neil, MD

Dr O'Neil is Professor of Medicine and Director of the Phase I and GI Malignancies Programs at Indiana University Simon Cancer Center in Indianapolis, Indiana.

Tracks 1-8

Track 1	Anti-angiogenic therapies for advanced hepatocellular carcinoma (HCC)	Track 5	Investigation of bevacizumab-based therapies in advanced HCC
Track 2	Results of a Phase III trial of sorafenib versus sunitinib in advanced HCC	Track 6	Mechanism of action of ramucirumab in HCC
Track 3	Combination of sorafenib with chemo-therapy or TACE for advanced HCC	Track 7	Potential roles of mTOR, MET and checkpoint inhibitors in HCC
Track 4	Use of sorafenib in patients with HCC and Child-Pugh B versus Child-Pugh C disease	Track 8	Therapeutic options for patients with sorafenib-refractory advanced HCC

Select Excerpts from the Interview

Tracks 2, 4

DR LOVE: Would you discuss the results of the Phase III trial of sunitinib versus sorafenib for patients with advanced hepatocellular carcinoma (HCC) and why we observe differences in outcomes between these 2 tyrosine kinase inhibitors?

DR O'NEIL: Considering what we observed in renal cell cancer, it was a surprise to many of us that sorafenib would come out so much ahead of sunitinib in this trial (Cheng 2013; [4.1]). The investigators were hoping that sunitinib would be better, but that was clearly not the case.

These are complicated drugs, and they have nonoverlapping tyrosine kinase targets. I'd love to know which targets are responsible. Candidates for sorafenib are RAF, CRAF or perhaps mutant BRAF, and although we haven't seen much of it in HCC, some RAF-driven mechanisms may be at work in this disease. It's difficult to pin everything on RAF because we have studied MEK inhibitors, and we published the first MEK inhibitor study in HCC and didn't see much activity (O'Neil 2011).

DR LOVE: What is your approach to the role and dosing of sorafenib for patients with HCC and Child-Pugh B versus Child-Pugh C disease?

DR O'NEIL: Because we don't have many other options, physicians have tended to treat somewhat outside of the criteria of the SHARP trial (Llovet 2008). In the GIDEON study the median survival for the patients with Child-Pugh B disease was only approximately 5 months (Marrero 2011). We can't say without a randomization whether that would be worse without sorafenib, but if you're a purist you can argue that it's a poor

4.1

Phase III Study* Evaluating Whether Sunitinib was Superior or Equivalent to Sorafenib in Advanced Hepatocellular Carcinoma

	Sunitinib	Sorafenib	Hazard ratio	Two-sided *p*-value
Median overall survival, ITT population (n = 530, 544)	7.9 mo	10.2 mo	1.30	0.0014
Asian regions (n = 402, 410)	7.7 mo	8.8 mo	1.21	NR
Ex-Asian regions (n = 128, 134)	9.3 mo	15.1 mo	1.64	NR
	Sunitinib (n = 526)		**Sorafenib** (n = 542)	
Select adverse events	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	50.8%	29.7%	17.3%	3.6%
Hand-foot syndrome	44.3%	13.3%	60.9%	21.3%
Neutropenia	36.5%	25.7%	4.6%	2.2%
Anemia	35.9%	9.3%	11.3%	4.0%
Fatigue	32.7%	6.3%	21.0%	3.9%
Leukopenia	31.7%	13.2%	7.9%	0.2%
Nausea	24.7%	1.1%	17.3%	0.9%

* Study was halted because of higher incidence of serious adverse events with sunitinib
ITT = intention to treat; NR = not reported

Cheng AL et al. *J Clin Oncol* 2013;31(32):4067-75.

survival rate with treatment and perhaps these patients would be better off without the side effects.

However, it's difficult to tell a patient, "No, we have absolutely nothing for you," and I believe that if patients understand what the side effects are and would rather try it, many of us would offer sorafenib. I draw the line at Child-Pugh C disease, but with Child-Pugh B disease we see a large range of outcomes, and some patients should have the opportunity to receive therapy.

Track 7

DR LOVE: Are you excited about any other agents or strategies under evaluation in HCC?

DR O'NEIL: I believe that c-MET inhibitors have generated the most excitement recently (Venepalli 2013). Data indicate that patients with c-MET-positive tumors have a somewhat worse prognosis. When they receive a c-MET inhibitor, they fare better.

Phase III studies are now ongoing — I believe tivantinib is the "first one out of the gate," but several other c-MET inhibitors are being studied, as are a couple of different antibodies, including onartuzumab (MetMAb) and rilotumumab. It will be interesting to see which of these strategies emerge as more effective. This mechanism will be intriguing over the next few years.

Immunotherapy has been effective in the adjuvant setting for HCC (Hui 2009). HCC is behind other tumors in terms of newer immunotherapeutic strategies such as PD-1 or PD-L1 inhibitors, but I'm hopeful that those will be broadly active and that we'll see some new developments in that space soon.

Track 8

DR LOVE: What are some of the most frequent questions oncologists ask about HCC?

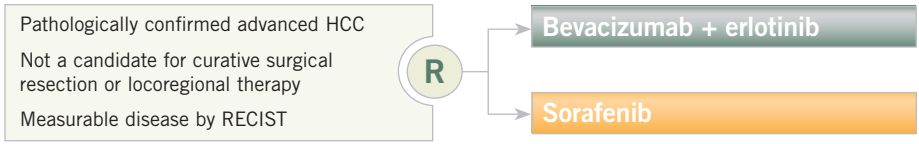
DR O'NEIL: What comes up the most is, "What do I do with a patient whose disease has progressed while he or she was receiving sorafenib?" I believe the options in that case include chemotherapy. We observe responses to chemotherapy occasionally, although I believe we don't have much proof that it improves survival. For a young patient with no other options, capecitabine, CAPOX or GEMOX can be considered.

Some investigators have also been interested in using bevacizumab/erlotinib, even though that combination regimen has not been subjected to Phase III studies yet. I believe that's an option for patients who don't have access to a trial, because the results from the single-arm Phase II study were compelling (Thomas 2009). Objective responses were clearly observed, in addition to an interesting median overall survival. A randomized Phase II study comparing bevacizumab/erlotinib to sorafenib has been ongoing for some time now, and we are looking forward to seeing the data (NCT00881751; [4.2]).

I have used bevacizumab/erlotinib sparingly outside of a trial setting. When I can, I enroll patients with sorafenib-refractory disease on clinical trials, but in the absence of such studies that's one of the options I have chosen. Perhaps 1 or 2 of my patients have benefited clinically from this regimen. It's not a home run, and in most patients with sorafenib-refractory disease for whom we've tried this regimen, we have not observed responses. ■

4.2 **Randomized Phase II Trial of Bevacizumab and Erlotinib Compared to Sorafenib as First-Line Therapy for Patients with Advanced Hepatocellular Carcinoma (HCC)**

Protocol ID: NCT00881751 **Target Accrual:** 120 (Open)



www.clinicaltrials.gov, November 2013.

SELECT PUBLICATIONS

Hui D et al. **A randomized, controlled trial of postoperative adjuvant cytokine-induced killer cells immunotherapy after radical resection of hepatocellular carcinoma.** *Dig Liver Dis* 2009;41(1):36-41.

Llovet JM et al. **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* 2008;359(4):378-90.

Marrero JA et al. **Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON) second interim analysis in more than 1,500 patients: Clinical findings in patients with liver dysfunction.** *Proc ASCO* 2011;**Abstract 4001**.

O'Neil BH et al. **Phase II study of the mitogen-activated protein kinase 1/2 inhibitor selumetinib in patients with advanced hepatocellular carcinoma.** *J Clin Oncol* 2011;29(17):2350-6.

Thomas MB et al. **Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma.** *J Clin Oncol* 2009;27(6):843-50.

Venepalli NK, Goff L. **Targeting the HGF-cMET axis in hepatocellular carcinoma.** *Int J Hepatol* 2013;2013:341636.