INTERVIEW

Philip A Philip, MD, PhD

Dr Philip is Professor of Oncology and Medicine, Director of GI and Neuroendocrine Tumors and Vice President of Medical Affairs at Wayne State University's Karmanos Cancer Institute in Detroit, Michigan.

Tracks 1-13

Select Excerpts from the Interview

Track 2

DR LOVE: What is your treatment approach for a patient with hepatocellular cancer (HCC) who is not a candidate for liver-directed therapy?

DR PHILIP: If a patient is deemed to be ineligible for liver-directed therapy, my next step is to administer sorafenib. The challenge here is that the patient who will not qualify for liver-directed therapy may also not have been represented on the SHARP trial (Abou-Alfa 2006), which included patients with Child-Pugh A disease and favorable performance statuses.

The question is, do you start these patients with a full or lower dose of sorafenib? This should be a personalized decision with each patient. I rarely administer sorafenib to patients with Child-Pugh C disease. For patients with Child-Pugh B disease, especially

the older patients, I tend to start with lower doses ranging from 200 to 600 mg. The key aspect here is to follow up frequently early on because I've seen patients in whom nontolerance can be discovered within a week or 2 of starting treatment.

Track 4

DR LOVE: What is your view on the use of therapies targeting the VEGF pathway in advanced HCC?

DR PHILIP: In HCC we believe that hypervascularity on a CAT or MRI scan translates into overactivation of the VEGF/VEGF receptor (VEGFR) pathway. We use liver-directed therapy because of the belief in the need to address the vascularity-related issues.

Ramucirumab is an interesting anti-VEGFR-2 monoclonal antibody. Before the ramucirumab era, bevacizumab initially showed benefit in a pilot study (Britten 2012), but in the randomized Phase II trials that followed, it failed to demonstrate much activity. Ramucirumab might prove to be a different and better agent because it targets the VEGF receptor rather than the growth factor itself and so has the potential to be effective.

The REACH trial of ramucirumab and best supportive care versus placebo/best supportive care as second-line therapy for patients with HCC after failure of first-line sorafenib is ongoing (2.1). Several agents, such as brivanib, have been tested after disease progression on sorafenib and have failed to be effective (Llovet 2013). Because sorafenib is a multikinase inhibitor that also targets VEGFR-2, it is unknown if its activity results from anti-angiogenesis. Although targeting the VEGF pathway is interesting, we do not know if ramucirumab after sorafenib failure will lead to major breakthroughs in the management of HCC.

Regorafenib is an oral small molecule anti-angiogenic agent being studied in the RESORCE trial in the second-line setting after sorafenib failure (2.1). Because both sorafenib and regorafenib inhibit VEGFR-2, among other targets, an important question to ask is whether they differ so much that regorafenib can elicit activity after sorafenib failure. At this time, we are in need of active agents targeting other biomarkers besides VEGF and VEGFRs.

2.1

Ongoing Trials of Anti-VEGF-Based Therapies for Patients with Advanced Hepatocellular Cancer

Trial ID	Phase	N	Setting	Treatment arms
NCT01140347 (REACH)	III	565	Second line (after sorafenib)	• Ramucirumab + BSC • Placebo + BSC
NCT01774344 (RESORCE)	III	530	Second line (after sorafenib)	• Regorafenib + BSC • Placebo + BSC
NCT02082210	I/II	55	Advanced	• Ramucirumab + LY2875358
NCT02069041	IB	9	Advanced	• Ramucirumab + FOLFOX4

BSC = best supportive care

www.clinicaltrials.gov. Accessed May 2014.

Tracks 7-8

DR LOVE: What factors do you consider when making a treatment decision for patients with metastatic pancreatic cancer (mPC) (Ghosn 2014; [2.2])?

DR PHILIP: The most important decision-making factor is the patient's performance status. I also consider age and liver function test results. I discuss the pros and cons of the treatment options with the patient, and their preference is important.

In my practice, about 10% to 15% of patients with unresectable or metastatic pancreatic cancer will receive gemcitabine alone, whereas 15% will receive FOLFIRINOX. Nowadays, the remaining 70% to 75% of patients will receive gemcitabine/*nab* paclitaxel.

I administer FOLFIRINOX to patients younger than age 75 with a performance status of 2 or lower and without major liver dysfunction. I don't believe any patients with mPC have a performance status of 0 because they all are symptomatic and have certain limitations. I do not administer FOLFIRINOX to any patient with elevations in bilirubin levels. I may consider administering FOLFIRINOX for patients with borderline enzyme elevations 2 or fewer times the upper limit of normal.

DR LOVE: In your experience, what are the side effects of gemcitabine/*nab* paclitaxel (Ghosn 2014; [2.2])?

DR PHILIP: Initially, patients may experience Grade II fatigue and myelosuppression. Continued treatment for longer periods is associated with increased fatigue and cumulative myelosuppression. In this situation, we may dose reduce by 20% while carefully monitoring symptoms as treatment is continued. If symptoms don't improve, I would administer therapy biweekly at the reduced dose.

2.2

Efficacy and Safety Results Across Trials of 3 FDA-Approved Regimens for Metastatic Pancreatic Cancer

Trial (authors)	Regimens evaluated	ORR	Median OS	Median PFS
ACCORD-11/0402 (Conroy et al)[1]	FOLFIRINOX	31.6%	11.1 mo	6.4 mo
	Gem	9.4%	6.8 mo	3.3 mo
MPACT (Von Hoff et al)[2]	Gem/*nab* pac	23%	8.5 mo	5.5 mo
	Gem	7%	6.7 mo	3.7 mo
Adverse events (≥Grade 3)[3]		**FOLFIRINOX**[1]	**Gem**[1]	**Gem/*nab* pac**[2]
Neutropenia		45.7%	21%	38%
Febrile neutropenia		5.4%	1.2%	3%
Thrombocytopenia		9.1%	3.6%	13%
Fatigue		23.6%	17.8%	17%
Diarrhea		12.7%	1.8%	6%
Peripheral neuropathy		9.0%	0%	17%

ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Gem = gemcitabine; *nab* pac = *nab* paclitaxel

[1] Conroy T et al. *N Engl J Med* 2011;364(19):1817-25; [2] Von Hoff DD et al. *Proc ASCO* 2013;**Abstract 4005**; [3] Ghosn M et al. *World J Gastroenterol* 2014;20(9):2352-7.

In my practice, neurotoxicity has not posed much of a problem with *nab* paclitaxel use during the first 6 months of therapy. This may be because we commonly dose reduce and are more proactive with managing the associated side effects. However, with extended treatment beyond this time, patients may experience some neurotoxic effects.

Track 9

DR LOVE: What is the status of the Phase II RECAP trial of capecitabine with or without ruxolitinib as second-line therapy for mPC?

DR PHILIP: Ruxolitinib targets the JAK-STAT pathway, which plays a key role in the signaling of many cytokines and growth factors. A recent press release reported that ruxolitinib was beneficial for a subset of patients on the RECAP trial (2.3). It is probable that those patients have disease that is characterized by a higher or constitutional activity of the circulating cytokines.

A biomarker that relates to cytokine release is serum C-reactive protein (CRP). I have been conducting tests to determine serum CRP levels in my patients for the past few weeks, and the results are interesting. The normal level is 9 ng/mL, but one of my patients expressed a level of 132 ng/mL and another had 10 ng/mL. It is reasonable to expect a spread in the CRP levels because some patients with pancreatic cancer have constitutional symptoms such as leukocytosis. Such patients possibly will benefit from ruxolitinib therapy. Hopefully, the results from the RECAP trial will be presented soon. (Editor's note: Subsequent to this interview results of the RECAP trial were presented [Hurwitz H et al. *Proc ASCO* 2014;**Abstract 4000**].) ■

2.3

Phase II RECAP Trial of Capecitabine with or without Ruxolitinib as Second-Line Therapy for Patients with Refractory Metastatic Pancreatic Cancer

Protocol ID: NCT01423604

Target accrual (n = 138)

- Metastatic pancreatic cancer (mPC)
- Karnofsky performance status ≥60
- Failure of first-line gemcitabine for mPC **or** other first-line chemotherapy for patients intolerant to or ineligible for gemcitabine

R

- Ruxolitinib + capecitabine
- Placebo + capecitabine

www.clinicaltrials.gov. Accessed May 2014.

Press release (8/21/13): "Results of the RECAP trial provide the first evidence that JAK inhibition is active in this disease and suggest a demonstrable survival benefit in a well-defined group of patients with refractory metastatic pancreatic cancer who can be identified without the development of a companion diagnostic test."

SELECT PUBLICATIONS

Abou-Alfa GK et al. **Phase II study of sorafenib in patients with advanced hepatocellular carcinoma.** *J Clin Oncol* 2006;24(26):4293-300.

Britten CD et al. **Transarterial chemoembolization plus or minus intravenous bevacizumab in the treatment of hepatocellular cancer: A pilot study.** *BMC Cancer* 2012;12:16.

Llovet JM et al. **Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: Results from the randomized phase III BRISK-PS study.** *J Clin Oncol* 2013;31(28):3509-16.