INTERVIEW

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Tracks 1-12

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Track 2 Use of the remove-avoid-apply-report model for management of sorafenib-related hand-foot syndrome in HCC

Track 3 Common sorafenib-related toxicities in HCC

Track 4 Use of sorafenib in advanced Child-Pugh B HCC

Track 5 GIDEON study: A global investigation of therapeutic decisions by oncologists and hepatologists on the use of sorafenib in the management of HCC

Track 6 Termination of a Phase III trial of sorafenib versus sunitinib in advanced HCC due to sunitinib-associated safety concerns

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Track 2

DR LOVE: What new developments have been reported in the management of side effects of systemic therapy for hepatocellular carcinoma (HCC)?

DR ABOU-ALFA: Without question one of the big challenges has been the management of side effects associated with sorafenib. The most common side effect is hand-foot syndrome. The second most common side effect is diarrhea, and the third is fatigue.

Dr Mario Lacouture at our institution has developed the remove, avoid, apply and report (RAAR) model that ensures that any potential skin damage is managed before treatment with sorafenib. RAAR recommends removing any calluses and allowing the skin to be well healed and not dry; avoiding items that can cause skin abrasion such as chemicals, hot water or scrubbing; applying moisturizers and taking pain medications, as needed; and most important, reporting all signs and symptoms immediately (Gish 2010; Lacouture 2008; [3.1]).

We pride ourselves at Memorial Sloan-Kettering Cancer Center that our patients do not develop hand-foot syndrome that is worse than Grade 2 because they receive clear

instructions after they start therapy. Within 2 to 3 days we are on the telephone with them and we are in the clinic within 7 days so we can circumvent any issue that may arise.

3.1 **The RAAR Model for Management of Sorafenib-Related Hand-Foot Skin Reactions**

Remove	calluses and hyperkeratotic regions
Avoid	factors that may aggravate the condition, such as sunlight, direct friction, hot water, constrictive footwear and cleaning products containing strong chemicals
Apply	moisturizers and cold packs
Report	signs of hand-foot skin reaction early

Gish RG et al. *Gastroenterol Hepatol* (NY) 2010;6(9 Suppl 16):1-16; Lacouture ME et al. *Oncologist* 2008;13(9):1001-11.

Tracks 6, 9

DR LOVE: What promising novel agents are under investigation in HCC?

DR ABOU-ALFA: Some anti-angiogenic agents are still in the running and are generating interest. Sunitinib is out, however, based on some disappointing results recently reported by Ann-Lii Cheng at ASCO. That Phase III study demonstrated a higher median overall survival with sorafenib as compared to sunitinib in patients with advanced HCC (Cheng 2011; [3.2]). However, this study was interesting because it was able to reproduce results reported with sorafenib in the Phase III SHARP trial, which compared sorafenib to placebo (Llovet 2008).

DR LOVE: What do we know about bevacizumab in HCC?

DR ABOU-ALFA: Bevacizumab has been studied extensively and appears to have some activity in HCC, but bleeding concerns are not to be ignored (Siegel 2008). Nonetheless, the addition of an anti-angiogenic agent to an EGFR inhibitor such as cetuximab or erlotinib may allow the combination to work synergistically.

The report from a single-arm study of a median overall survival of 15.7 months with bevacizumab/erlotinib in advanced HCC was impressive (Thomas 2009), making the Phase II study of bevacizumab/erlotinib versus sorafenib an appropriate scientific approach (3.3).

3.2 **Phase III Study* of Sunitinib versus Sorafenib in Advanced Hepatocellular Carcinoma**

	Sunitinib	Sorafenib	Hazard ratio	*p*-value
Median overall survival,				
ITT population (n = 530, 544)	7.9 mo	10.2 mo	1.30	0.0010
Asian regions (n = 402, 410)	7.7 mo	8.8 mo	1.21	0.0171
Ex-Asian regions (n = 127, 134)	9.3 mo	15.1 mo	1.64	0.0036

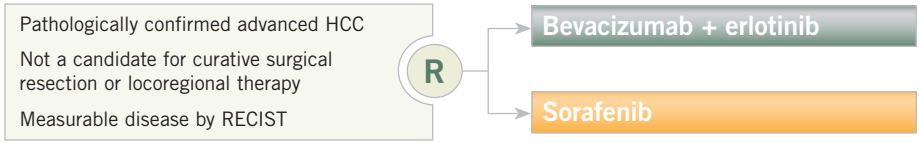
* Study was halted due to higher incidence of serious adverse events with sunitinib.

Cheng A et al. *Proc ASCO* 2011;**Abstract 4000**.

3.3

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

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



www.clinicaltrials.gov, April 2012.

Track 11

DR LOVE: Would you discuss the biology of biliary tract cancers and your approach to treating these diseases?

DR ABOU-ALFA: Even though the biology may differ, bile duct and gallbladder cancers are often lumped together. The ABC-02 trial previously reported that gemcitabine in combination with cisplatin improves survival versus gemcitabine alone (Valle 2010; [3.4]), and this combination is currently the standard for patients with advanced biliary cancers. Interestingly enough, that approach has been evolving because we see a tolerance issue with regard to how much cisplatin can be administered. This has given rise to an interest in combination therapies. I am currently involved in a study evaluating gemcitabine/cisplatin and sorafenib for patients with advanced biliary tract cancers (NCT00919061). Data from this study should be published soon. ■

3.4

UK ABC-02 Trial: Gemcitabine (Gem) with or without Cisplatin (Cis) for Patients with Advanced or Metastatic Biliary Tract Cancer

	Gem (n = 206)	Gem + Cis (n = 204)	Hazard ratio	*p*-value
Median overall survival	8.1 mo	11.7 mo	0.64	<0.001
Median progression-free survival	5.0 mo	8.0 mo	0.63	<0.001

Valle J et al. *N Engl J Med* 2010;362(14):1273-81.

SELECT PUBLICATIONS

Cheng A et al. **Phase III trial of sunitinib (Su) versus sorafenib (So) in advanced hepatocellular carcinoma (HCC).** *Proc ASCO* 2011;**Abstract 4000**.

Gish RG et al. **Integrating recent data in managing adverse events in the treatment of hepatocellular carcinoma.** *Gastroenterol Hepatol* (NY) 2010;6(9 Suppl 16):1-16.

Lacouture ME et al. **Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib.** *Oncologist* 2008;13(9):1001-11.

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

Siegel AB et al. **Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma.** *J Clin Oncol* 2008;26(2):2992-8.

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.

Valle J et al. **Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer.** *N Engl J Med* 2010;362(14):1273-81.