



## INTERVIEW

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#### Tracks 1-11

- Track 1** Critical assessment of local treatment modalities in hepatocellular carcinoma (HCC)
- Track 2** Results from a Phase II trial of Bead Block® microspheres versus doxorubicin-eluting beads for arterial embolization of HCC
- Track 3** Response assessment and complications associated with chemoembolization of HCC
- Track 4** Transarterial chemoembolization with or without sorafenib in HCC
- Track 5** Survival advantage with the addition of sorafenib to doxorubicin for advanced HCC
- Track 6** Use of sorafenib in patients with HCC and Child-Pugh B disease
- Track 7** Management of sorafenib-associated hand-foot syndrome
- Track 8** Investigation of anti-angiogenic agents in HCC
- Track 9** Heterogeneity of biliary tract cancers and opportunities for development of novel treatments
- Track 10** **Case discussion:** A 78-year-old patient presents with abdominal pain and is diagnosed with HCC and bone metastases
- Track 11** CALGB-80802: A Phase III trial of sorafenib alone versus sorafenib/doxorubicin for advanced HCC

## Select Excerpts from the Interview

### Tracks 1-4

► **DR LOVE:** What are your thoughts on the use of chemoembolization versus systemic therapy for patients with advanced hepatocellular carcinoma (HCC)?

► **DR ABOU-ALFA:** Embolization or transarterial chemoembolization (TACE) is used for patients with extensive liver disease, tumors with close proximity to blood vessels or those that are unresectable. Systemic therapy with sorafenib would be recommended for patients with metastatic disease or unresectable local disease that is not amenable to therapy with embolization or TACE or for patients for whom prior therapy has failed.

Several years ago studies by Llovet (Llovet 2002) and Lo (Lo 2002) reported a survival benefit with TACE versus best supportive care, but it applied to relatively small disease in the liver. Notably, the study by Llovet and colleagues was discontinued early and the benefit of bland embolization versus best supportive care could not be determined.

Bland embolization has evolved with time, and we now try to achieve embolization to stasis to block off all the blood supply to the tumor. At the 2013 Gastrointestinal Cancers Symposium our group presented a randomized Phase II trial comparing bland embolization to chemoembolization with drug-eluting beads (Brown 2013; [4.1]). This

was probably the first study that directly compared chemoembolization to embolization. The most common side effect was postembolization syndrome, which is a classic syndrome of fever, pain and elevated liver function test results. As expected, certain side effects related to doxorubicin were observed on the chemoembolization arm.

The study reported no difference between the 2 arms, calling into question the addition of chemotherapy to embolization. The median overall survival for embolization versus chemoembolization was 16.6 and 19.6 months, respectively, which is much shorter than what was previously reported. Nowadays, we are expanding the scope of embolization to larger lesions, and that may account for the shorter survival. We may have to expand the role of systemic therapy to include not only patients with metastatic disease but also those with locally advanced disease that is beyond the scope of embolization.

► **DR LOVE:** What are your thoughts on the combination of sorafenib with TACE for the treatment of HCC?

► **DR ABOU-ALFA:** Recently, the large, randomized, Phase II SPACE trial reported no improvement in outcome with the addition of sorafenib to TACE for patients with HCC (Lencioni 2012). The combination of sorafenib and TACE is being further evaluated in 2 ongoing studies, ECOG-E1208 (NCT01004978) and TACE-2 (NCT01324076). Currently the data do not support the use of anti-angiogenic therapy after embolization.

#### 4.1

#### Results from a Randomized Phase II Trial of Bead Block Microspheres versus Doxorubicin-Eluting Beads for Arterial Embolization of Hepatocellular Carcinoma

- This Phase II study reported that doxorubicin-eluting beads did not improve response rate, median time to disease progression, progression-free survival or overall survival.
- The addition of doxorubicin to the beads did not increase toxicity or compromise safety.
- The authors contend that the results from this study call into question added benefit of chemotherapy for embolization of hepatocellular carcinoma.

Brown KT et al. Gastrointestinal Cancers Symposium 2013; **Abstract 143**.

#### Tracks 5-7

► **DR LOVE:** Would you discuss the combination of doxorubicin and sorafenib for patients with advanced HCC?

► **DR ABOU-ALFA:** We investigated the combination of sorafenib with doxorubicin versus doxorubicin/placebo in the first-line setting for patients with advanced HCC. The study reported a significant improvement in overall survival for the doxorubicin/sorafenib arm, with a median survival of 13.7 months compared to 6.5 months for doxorubicin/placebo (Abou-Alfa 2010; [4.2]). The results with doxorubicin alone were expected, but the study raised the question of possible synergy between doxorubicin and sorafenib that could account for the 13.7-month median survival versus 10.7 months, which is what is reported for sorafenib.

That question is being addressed by the CALGB-80802 study, which is the first NCI-sponsored Phase III trial in HCC in the United States. This trial comparing

### Randomized Phase II Trial of Doxorubicin (Dox) in Combination with Sorafenib versus Dox Alone for Advanced Hepatocellular Carcinoma

Survival	Dox + sorafenib (n = 47)	Dox + placebo (n = 49)	Hazard ratio	p-value
Median time to progression	6.4 mo	2.8 mo	0.5	0.02
Median overall survival	13.7 mo	6.5 mo	0.49	0.006
Median progression-free survival	6.0 mo	2.7 mo	0.54	0.006
Select adverse events (Grade 3 or 4)	Dox + sorafenib (n = 47)	Dox + placebo (n = 49)		
Any adverse event	63.8%	60.4%		
Constitutional symptoms	6.4%	6.3%		
Fatigue	6.4%	6.3%		
Dermatologic	10.6%	0%		
Hand-foot skin reaction	6.4%	0%		
Gastrointestinal	21.3%	18.8%		
Hematologic	44.7%	50.1%		
Infection	0%	8.3%		
Pain	6.4%	0%		

Abou-Alfa GK et al. *JAMA* 2010;304(19):2154-60.

doxorubicin and sorafenib to sorafenib alone for patients with locally advanced or metastatic HCC is ongoing (4.3).

At the 2012 Gastrointestinal Cancers Symposium we presented data from a retrospective study evaluating the addition of doxorubicin to sorafenib therapy in 14 patients for whom sorafenib had failed (Abou-Alfa 2012). It is intriguing that in comparison to historical controls the median survival almost doubled with second-line doxorubicin/sorafenib after failure of sorafenib. A Phase II study, due to start soon, will further investigate the addition of doxorubicin to sorafenib after failure to respond to sorafenib in the first line.

► **DR LOVE:** What are the recommendations for sorafenib use in patients with HCC who have Child-Pugh B disease?

► **DR ABOU-ALFA:** A retrospective analysis of data from a Phase II study evaluating sorafenib in patients with Child-Pugh B disease and advanced HCC reported a

### CALGB-80802: A Phase III Study of Sorafenib with or without Doxorubicin for Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

Protocol ID: NCT01015833

Target accrual: 480

#### Eligibility

- Locally advanced or metastatic HCC
- Unresectable or transplant ineligible
- Child-Pugh score A

R

Sorafenib + doxorubicin

Sorafenib

[www.clinicaltrials.gov](http://www.clinicaltrials.gov), July 2013.

worsening of liver function on sorafenib therapy (Abou-Alfa 2011). The CALGB-60301 trial evaluated the safety of sorafenib in patients with advanced hepatic or renal dysfunction (Miller 2009). The dose-limiting toxicity was an increase in bilirubin, which occurred more frequently in the patients with elevated bilirubin at baseline. The study made recommendations regarding the starting sorafenib dose in these patients.

Patients with bilirubin levels of 1.5 times the upper limit of normal or lower should receive the full dose of sorafenib — 400 mg BID. Patients with bilirubin levels of 1.5 to 3 times the upper limit of normal should receive half that dose — 200 mg BID. For patients with bilirubin levels more than 3 times the upper level of normal, no safe dose has been reported. For patients with albumin levels less than 2.5 mg/dL, regardless of the bilirubin level, sorafenib should be administered at 200 mg daily. These recommendations are not adopted by everyone. I use these guidelines because bilirubin levels can escalate quickly in a patient with Child-Pugh B disease who is receiving sorafenib.

► **DR LOVE:** Are you concerned about administering sorafenib to elderly patients or those with poor performance status?

► **DR ABOU-ALFA:** I'm not concerned about administering sorafenib to elderly patients with a good performance status. A poor performance status could be related to liver function in a patient with cirrhosis and would argue against sorafenib use in some cases.

► **DR LOVE:** How do you manage the hand-foot skin reaction associated with sorafenib?

► **DR ABOU-ALFA:** A large Phase II study evaluated the prophylactic effect of a urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced HCC (Ren 2012). The study reported that the urea-based cream reduced the incidence and severity of hand-foot skin reaction. However, there were some caveats to the study with regard to how the assessments were performed and the fact that the study was not blinded. Hand-foot syndrome is still not completely understood and remains an active area of research. ■

## SELECT PUBLICATIONS

Abou-Alfa GK et al. **Retrospective review of doxorubicin plus sorafenib as second-line therapy in hepatocellular carcinoma (HCC).** *Gastrointestinal Cancers Symposium* 2012;**Abstract 298.**

Abou-Alfa GK et al. **Safety and efficacy of sorafenib in patients with hepatocellular carcinoma (HCC) and Child-Pugh A versus B cirrhosis.** *Gastrointest Cancer Res* 2011;4(2):40-4.

Brown KT et al. **A randomized single blind controlled trial of beads versus doxorubicin-eluting beads for arterial embolization of hepatocellular carcinoma (HCC).** *Gastrointestinal Cancers Symposium* 2013;**Abstract 143.**

Lencioni R et al. **Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial.** *Gastrointestinal Cancers Symposium* 2012;**Abstract LBA154.**

Llovet JM et al. **Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial.** *Lancet* 2002;359(9319):1734-9.

Lo CM et al. **Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma.** *Hepatology* 2002;35(5):1164-71.

Miller A et al. **Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301.** *J Clin Oncol* 2009;27(11):1800-5.

Ren Z et al. **A randomized controlled phase II study of the prophylactic effect of urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced hepatocellular carcinoma.** *Proc ASCO* 2012;**Abstract 4008.**