INTERVIEW

Johanna C Bendell, MD

Dr Bendell is Director of GI Oncology Research and Associate Director of the Drug Development Unit at Sarah Cannon Research Institute in Nashville, Tennessee.

Tracks 1-19

Select Excerpts from the Interview

Track 3

DR LOVE: The ToGA trial previously demonstrated a survival advantage with the addition of trastuzumab to chemotherapy for patients with HER2-positive advanced gastric cancer (GC). What other HER2-targeted therapies are currently under investigation in HER2-positive GC?

DR BENDELL: T-DM1 is currently under investigation as second-line therapy for advanced disease (2.1). We're excited about T-DM1 in GC as well as the data coming from studies of pertuzumab combined with trastuzumab. Additional ongoing studies are investigating anti-HER2 therapies in the first-line and locally advanced settings.

2.1

Select Ongoing Clinical Trials of HER2-Directed Therapies in Gastric Cancer (GC), Including Adenocarcinoma of the Gastroesophageal Junction (GEJ)

Trial ID	Phase	Treatment arms	Patient population
NCT01641939	III	• T-DM1 (3.6 mg/kg, q3wk) • T-DM1 (2.4 mg/kg, q1wk) • Taxane	Previously treated locally advanced or metastatic GC
NCT01774786	III	• Pertuzumab/trastuzumab/CT • Placebo/trastuzumab/CT	Chemotherapy and HER2-directed therapy-naïve metastatic GC or GEJ
NCT01702558	II	• T-DM1/capecitabine	Previously treated locally advanced or metastatic GC
NCT01191697	II	• Trastuzumab/CAPOX/bev	Metastatic GEJ

CT = chemotherapy; bev = bevacizumab

www.clinicaltrials.gov, June 2013.

Tracks 4-5

DR LOVE: Would you discuss the results of the Phase III REGARD trial evaluating second-line ramucirumab for metastatic GC or gastroesophageal junction cancer (Fuchs 2013; [2.2])?

DR BENDELL: Ramucirumab is a fully human monoclonal antibody directed against VEGFR-2. Whereas bevacizumab binds to the ligand, ramucirumab binds to the receptor. In the REGARD study, patients were randomly assigned to receive ramuci-

2.2

REGARD: A Phase III, Randomized, Double-Blind Trial of Ramucirumab and Best Supportive Care (BSC) versus Placebo and BSC as Second-Line Therapy for Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Efficacy	Ramucirumab (n = 238)	Placebo (n = 117)	Hazard ratio	Log-rank *p*-value
Median overall survival	5.2 mo	3.8 mo	0.776	0.0473
Median progression-free survival	2.1 mo	1.3 mo	0.483	<0.0001
Response rate (CR + PR)	3.4%	2.6%	—	0.756
Select adverse events, Grade ≥3	**Ramucirumab** (n = 236)		**Placebo** (n = 115)	
Fatigue	6.4%		9.6%	
Hypertension	7.6%		2.6%	
Anemia	6.4%		7.8%	

CR = complete response; PR = partial response

Fuchs S et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA5**.

rumab or placebo. Improvements were observed in overall and progression-free survival with ramucirumab. A few years ago, data from the AVAGAST study of capecitabine/cisplatin with or without bevacizumab as first-line therapy for patients with GC reported no improvements in overall survival (Ohtsu 2011). However, on subgroup analysis, particularly of patients in the United States, a significant trend toward improvement in overall and progression-free survival was observed with bevacizumab.

Differences in the epidemiology of GC worldwide have been discussed. In the United States, GC with much poorer prognosis tends to be present, which, for unknown reasons, appears to be more susceptible to anti-angiogenic agents. In the REGARD study, most patients received ramucirumab in North America. This may explain why the REGARD study was positive, whereas AVAGAST wasn't.

We're awaiting results from 2 other studies: The RAINBOW trial, which is evaluating second-line paclitaxel with or without ramucirumab, and a first-line Phase II study of FOLFOX with or without ramucirumab. Patients with metastatic gastroesophageal cancer definitely need more treatment options. Most patients don't make it to second-line therapy, and those who do have a poor survival of approximately 4 months. The availability of more agents should result in a better survival.

Tracks 15-16

DR LOVE: Given the new options for continued angiogenic inhibition after progression on first-line therapy, how do you approach the treatment of metastatic colorectal cancer (mCRC)?

DR BENDELL: The ARIES (Bendell 2012) and BRiTE (Grothey 2008) registrational trials initially investigated bevacizumab beyond progression, and benefits in the TML study (2.3) weren't as robust as those observed in ARIES or BRiTE. This suggests that doctors can select patients who are benefiting from anti-angiogenic therapy better than the trials. The patients who benefit from bevacizumab beyond first progression are those for whom up-front bevacizumab-based chemotherapy was beneficial and well tolerated. The decision for bevacizumab continuation as second-line therapy boils down to individual patient outcomes in the first line.

If a patient fared well with bevacizumab-based chemotherapy, such as FOLFOX, in the first-line setting, then I'm more inclined to continue bevacizumab with FOLFIRI into the second line. If a patient experienced rapid progression on first-line bevacizumab-based therapy, I may consider switching up the anti-angiogenic agent to something like afliber-

2.3

ML18147: Results from a Phase III Trial Evaluating the Addition of Bevacizumab (Bev) to Crossover Fluoropyrimidine-Based Chemotherapy (CT) for Patients with Metastatic Colorectal Cancer Experiencing Disease Progression on First-Line CT/Bev

Efficacy	CT + bev (n = 409)	CT (n = 410)	Hazard ratio	*p*-value
Median overall survival	11.2 mo	9.8 mo	0.81	0.0062
Median progression-free survival	5.7 mo	4.1 mo	0.68	<0.0001

Bennouna J et al. *Lancet Oncol* 2013;14(1):29-37.

cept. And, although it's good to now have regorafenib as an available option for mCRC, we are far from being able to identify those patients who might best benefit from it.

Aflibercept in combination with FOLFIRI improved overall and progression-free survival in the Phase III VELOUR trial (2.4). In my practice, the major side effect associated with aflibercept is asthenia. I also observe an increased incidence of diarrhea and neutropenia.

In terms of regorafenib, I have been seeing a patient for 5 years who had received all systemic chemotherapies. He also participated in 3 Phase I trials for patients with refractory disease. I was running out of options when regorafenib received FDA approval. I initiated treatment and was thrilled because after 2 cycles of regorafenib, his CEA level dropped, he experienced a minor response and he is currently tolerating it well. Like sorafenib, the major side effects of regorafenib are fatigue and hand-foot syndrome (2.5). For the latter, I recommend a urea-based cream thrice daily.

2.4

VELOUR: A Phase III Trial of Aflibercept versus Placebo in Combination with FOLFIRI as Second-Line Therapy for Metastatic Colorectal Cancer

Survival	FOLFIRI + aflibercept (n = 612)	FOLFIRI + placebo (n = 614)	Hazard ratio	*p*-value
Median progression-free survival	6.9 mo	4.7 mo	0.758	<0.0001
Median overall survival	13.5 mo	12.1 mo	0.817	0.0032

Select adverse events (Grades 3-4)	FOLFIRI + aflibercept (n = 611)	FOLFIRI + placebo (n = 605)
Neutropenia	36.7%	29.5%
Asthenic conditions	16.8%	10.6%
Diarrhea	19.3%	7.8%

Van Cutsem E et al. *J Clin Oncol* 2012;30(28):3499-506.

2.5

CORRECT: A Phase III Trial of Regorafenib with Best Supportive Care (BSC) versus Placebo with BSC for Patients with Metastatic Colorectal Cancer Who Experience Disease Progression After Standard Therapies

Efficacy	Regorafenib + BSC (n = 505)	Placebo + BSC (n = 255)	Hazard ratio	*p*-value
Median overall survival	6.4 mo	5.0 mo	0.77	0.0052
Median progression-free survival	1.9 mo	1.7 mo	0.49	<0.0001
Disease control rate	41.0%	15%	—	<0.0001
	Regorafenib + BSC (n = 500)		**Placebo + BSC** (n = 253)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Hand-foot skin reaction	47%	16.6%	8%	0.4%
Fatigue	47%	9.6%	28%	5.1%

Grothey A et al. *Lancet* 2013;381(9863):303-12.

Track 18

DR LOVE: What are your thoughts on the results of the Phase III MPACT study of gemcitabine with or without weekly *nab* paclitaxel for metastatic pancreatic cancer?

DR BENDELL: This study showed that the *nab* paclitaxel/gemcitabine regimen is effective with overall and progression-free survival benefits (Von Hoff 2013; [2.6]). The MPACT study was conducted in a different patient population from the ACCORD-11 trial of FOLFIRINOX, which was conducted exclusively in France by investigators who understood and knew how to administer FOLFIRINOX. The ACCORD-11 study provided patients with growth factors and strong antiemetics and included adequate supportive care and dose reductions to manage toxicities.

DR LOVE: Typically, younger patients with metastatic pancreatic cancer are treated with FOLFIRINOX. Based on the results of the MPACT study, would you consider *nab* paclitaxel/gemcitabine as an option in this setting?

DR BENDELL: We were involved in the MPACT trial, but I would like to have more experience with *nab* paclitaxel/gemcitabine in terms of toxicities. The primary toxicities I observed were blood count issues, so I administered growth factors on occasion, not automatically as I do with FOLFIRINOX. I have also observed numbness, tingling and neuropathy but primarily hematologic toxicities. I would also like to get a personal feel for its efficacy compared to that of modified FOLFIRINOX. ■

2.6

MPACT: A Phase III Trial of Weekly *Nab* Paclitaxel (*nab*-P)/Gemcitabine (Gem) versus Gem Alone for Patients with Metastatic Pancreatic Cancer

Efficacy outcome	*nab*-P/Gem (n = 431)	Gem (n = 430)	Hazard ratio	*p*-value
Median OS	8.5 months	6.7 months	0.72	0.000015
Median PFS	5.5 months	3.7 months	0.69	0.000024
ORR (independent review)	23%	7%	—	1.1×10^{-10}
Grade ≥3 adverse events	***nab*-P/Gem** (n = 421)		**Gem** (n = 402)	
Neutropenia	38%		27%	
Leukopenia	31%		16%	
Fatigue	17%		7%	
Peripheral neuropathy	17%		<1%	

OS = overall survival; PFS = progression-free survival; ORR = overall response rate

Von Hoff DD et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA148**.

SELECT PUBLICATIONS

Bendell JC et al. **Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-bevacizumab or FOLFIRI-bevacizumab: Results from ARIES, a bevacizumab observational cohort study.** *Oncologist* 2012;17(12):1486-95.

Grothey A et al. **Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: Results from a large observational cohort study (BRiTE).** *J Clin Oncol* 2008;26(33):5326-34.

Ohtsu A et al. **Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A randomized, double-blind, placebo-controlled Phase III study.** *J Clin Oncol* 2011;29(30):3968-76.