INTERVIEW

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Tracks 1-11

Track 1	**Case discussion:** A 54-year-old non-smoker with a history of breast cancer presents with a squamous cell carcinoma of the esophagus
Track 2	Use of PET-CT to evaluate response to induction chemotherapy in esophageal cancer
Track 3	Addition of anti-EGFR antibodies to chemoradiation therapy and outcomes in esophageal cancer
Track 4	Investigation of immune checkpoint inhibitors in esophageal and gastric cancers
Track 5	**Case discussion:** A 50-year-old patient presents with weight loss, dysphagia and abdominal pain and is diagnosed with HER2-negative adenocarcinoma of the gastroesophageal junction (GEJ) with hepatic metastases
Track 6	Clinical experience with the recently FDA-approved agent ramucirumab as monotherapy or in combination with paclitaxel as second-line therapy for metastatic gastric or GEJ adenocarcinoma
Track 7	Phase II trial results and ongoing Phase III studies of ramucirumab as first-line therapy for advanced gastric or esophageal adenocarcinoma
Track 8	Trials of T-DM1 and pertuzumab in HER2-positive metastatic gastric cancer
Track 9	Treatment for patients with HER2-positive gastric cancer and disease progression on anti-HER2 therapy
Track 10	Investigation of regorafenib in combination with FOLFOX for patients with inoperable or metastatic gastroesophageal carcinoma
Track 11	Clinical experience with alternative schedules and doses of regorafenib

Select Excerpts from the Interview

Track 4

DR LOVE: Would you comment on the research investigating immune checkpoint inhibitors for patients with gastric or esophageal cancers?

DR ILSON: Anti-PD-1 and anti-PD-L1 inhibitors are being studied in gastroesophageal adenocarcinoma. Squamous cell carcinomas are rare, and they haven't been specifically studied in this context. Anecdotal responses to anti-PD-1/anti-PD-L1 agents have been noted. A signal of activity is observed, though it is not as strong as that with other cancers, such as lung cancer (Muro 2014).

I believe further evaluation in Phase II studies is of interest. Ongoing studies are evaluating anti-PD-1 and anti-PD-L1 drugs alone or in combination with CTLA-4 inhibitors. This is not a home run yet, but some patients may benefit from this strategy.

An interesting area of study, based on the abscopal effect, is administration of therapy to prime the immune response followed by radiation therapy to release antigens and enhance the immune response. We've seen much interest in sequencing radiation therapy with immune checkpoint inhibitors to determine if we can induce responses by creating an antigen burst. This is an exciting area of future research.

Track 6

DR LOVE: Would you discuss the results of the Phase III REGARD and RAINBOW trials investigating ramucirumab as second-line therapy for metastatic gastric or gastroesophageal junction (GEJ) cancer?

DR ILSON: The REGARD trial demonstrated that treatment with single-agent ramucirumab resulted in improvement in progression-free and overall survival versus placebo in the second-line setting for patients whose disease had progressed on fluoropyrimidine/platinum-based chemotherapy (Fuchs 2014). Ramucirumab monotherapy was approved by the FDA as second-line therapy based on these data. It was fairly well tolerated, and the only Grade 3 toxicity that was noteworthy was an increase in hypertension. Epistaxis was reported, but bleeding and gastrointestinal perforation were not serious adverse events.

The RAINBOW trial showed even more compelling data with ramucirumab in combination with paclitaxel. A significant improvement was observed in progression-free and overall survival with the combination. An almost 2-fold increase in response rate with the combination versus paclitaxel alone was also noted (Wilke 2014; [1.1]).

A slight increase in neutropenia was observed with the combination. Ramucirumab may augment some of the toxicity of chemotherapy, but that does not translate into clinically significant neutropenic fever. I believe that most practitioners would use ramucirumab in combination with paclitaxel, unless the patient has a poor performance status and cannot tolerate chemotherapy. In my practice, I generally administer the combination because taxanes are now standard second-line chemotherapy.

1.1

Efficacy Results of the Phase III REGARD and RAINBOW Trials of Ramucirumab (Ram) in Metastatic Gastroesophageal Junction and Gastric Adenocarcinoma After Disease Progression on First-Line Platinum- and/or Fluoropyrimidine-Containing Combination Therapy

	REGARD trial[1]		RAINBOW trial[2]	
Clinical outcome	Ram (n = 238)	Placebo (n = 117)	Ram + pac (n = 330)	Pac (n = 335)
Median OS	5.2 mo	3.8 mo	9.6 mo	7.4 mo
p-value	0.047		0.017	
Median PFS	2.1 mo	1.3 mo	4.4 mo	2.9 mo
p-value	<0.0001		<0.0001	
ORR	3%	3%	28%	16%
p-value	0.76		0.0001	

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

[1] Fuchs CS et al. *Lancet* 2014;383(9911):31-9; [2] Wilke H et al. *Lancet Oncol* 2014;15(11):1224-35.

Editor's Note: FDA Expands Approval for Ramucirumab for Advanced GEJ Cancer

Subsequent to this interview, on November 5, 2014, the FDA approved ramucirumab for use in combination with paclitaxel for the treatment of advanced gastric or GEJ adenocarcinoma.

Tracks 8-9

DR LOVE: What are your thoughts on therapies targeting HER2 for HER2-positive gastric cancer or GEJ cancer?

DR ILSON: Trastuzumab is approved in combination with a fluoropyrimidine/cisplatin as first-line therapy for patients with HER2-positive metastatic gastric or GEJ cancer. I generally administer trastuzumab in combination with chemotherapy because we have no data to support its use as monotherapy.

For patients who experience disease progression, extrapolating from data in breast cancer, I continue trastuzumab as second-line therapy. If patients experience rapid disease progression while receiving second-line therapy, it's difficult to rationalize continuing trastuzumab in the third-line setting.

Pertuzumab has been validated in breast cancer and is now being investigated in gastric cancer. The JACOB trial is an ongoing Phase III trial of chemotherapy/trastuzumab with or without pertuzumab as first-line therapy for patients with HER2-positive metastatic gastric or GEJ cancer with an estimated enrollment of more than 700 patients. In the second-line setting, the GATSBY trial is studying T-DM1 versus a taxane for patients with HER2-positive locally advanced or metastatic gastric cancer who have experienced disease progression during or after first-line therapy and has a target accrual of more than 400 patients (1.2).

A recent trial suggested benefit from lapatinib in Asian patients in the second-line setting (Satoh 2014). However, in Western patients, lapatinib in combination with capecitabine and oxaliplatin did not improve survival in the first-line setting (Hecht 2013). I believe that lapatinib is not likely to move forward in the West.

1.2

Ongoing Phase III Trials of HER2-Directed Therapies in HER2-Positive Locally Advanced or Metastatic Gastroesophageal Junction Cancer or Gastric Adenocarcinoma

Trial ID	N	Treatment arms
NCT01774786 (JACOB)	780	• Pertuzumab + TFP • Placebo + TFP
NCT01641939 (GATSBY)	412	• Triweekly T-DM1 (3.6 mg/kg) • Weekly T-DM1 (2.4 mg/kg) • Taxane (paclitaxel or docetaxel)
NCT00680901 (LOGiC)	545	• Lapatinib + CAPOX • Placebo + CAPOX

TFP = trastuzumab, cisplatin and fluoropyrimidine (capecitabine or 5-fluorouracil);
CAPOX = capecitabine/oxaliplatin

www.clinicaltrials.gov. Accessed December 2014.

Tracks 10-11

DR LOVE: What is the rationale behind the Phase II study of adjuvant regorafenib versus placebo for patients with node-positive esophageal or GEJ cancer who completed preoperative therapy?

DR ILSON: The impetus for this study came from a Phase II study of single-agent sorafenib in patients with metastatic esophageal or GEJ cancer who had received 1 or 2 prior lines of therapy. The median progression-free survival was approximately 4 months, with 1 durable complete remission reported with sorafenib (Ku 2013). Patients were receiving the agent for approximately 4 months, and some patients were able to continue therapy for 1 to 2 years.

Based on that signal, we're going to investigate regorafenib, an analogous drug, for patients with high-risk disease in the adjuvant setting. This study is being conducted through the Alliance and compares adjuvant regorafenib to placebo for patients with node-positive esophageal or GEJ cancer who have completed preoperative therapy (NCT02234180). We will prospectively explore potential biomarkers like VEGF-A. Our objective is to determine if we can significantly increase disease-free survival with this adjuvant approach.

DR LOVE: Regorafenib was approved for colorectal cancer in a late-line setting, but there have been concerns about toxicity. How do you manage regorafenib dosing to prevent toxicity?

DR ILSON: The recommended dose of regorafenib is 160 mg a day, 3 weeks on, 1 week off. Administering drugs that cause cutaneous toxicity 2 or 3 weeks in a row is often problematic. We are conducting a Phase II trial of regorafenib combined with FOLFOX as first-line therapy for unresectable or metastatic esophageal and gastric cancer (NCT01913639), and regorafenib will be administered for 1 week on, 1 week off. With this schedule, you achieve approximately 75% of the 160-mg daily dose, and we have observed virtually no toxicity.

My message to practitioners is to think about alternative doses and schedules. If patients start treatment on the full dose, they should be monitored every week for the first couple of months and dose reductions should be made promptly so that patients don't run into problems. ■

SELECT PUBLICATIONS

Hecht JR et al. **Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC trial.** *Proc ASCO* 2013;**Abstract LBA4001**.

Ku GY et al. **Phase II trial of sorafenib in esophageal (E) and gastroesophageal junction (GEJ) cancer: Response and prolonged stable disease observed in adenocarcinoma.** Gastrointestinal Cancers Symposium 2013;**Abstract 91**.

Muro K et al. **A phase 1b study of pembrolizumab (pembro; MK-3475) in patients (pts) with advanced gastric cancer.** *Proc ESMO* 2014;**Abstract LBA15**.

Satoh T et al. **Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN — A randomized, phase III study.** *J Clin Oncol* 2014;32(19):2039-49.

Yoon H et al. **Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial.** *Proc ASCO* 2014;**Abstract 4004**.