INTERVIEW

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Tracks 2-4

DR LOVE: Would you discuss the use of preoperative therapy for patients with esophageal cancer?

DR ILSON: Most cancer centers in the United States endorse chemotherapy and radiation therapy as preoperative treatments for gastric cancer. Two recent studies from Europe give weight to that approach. One study was a small, head-to-head comparison for patients with T3-4 adenocarcinoma of the

gastroesophageal (GE) junction and cardia. Patients were randomly assigned to receive three months of chemotherapy alone followed by surgery or chemotherapy and radiation therapy followed by surgery. Although it was an underpowered study, much higher rates of pathologic complete response were seen with chemoradiation therapy — approximately 16 percent — versus chemotherapy alone — two percent. Significant trends toward better survival in the chemoradiation therapy group were also reported (Stahl 2009).

The second trial that emphasized the value of preoperative chemoradiation therapy was a randomized trial of 363 patients with adenocarcinoma or squamous cancer (Gaast 2010). The trial compared surgery alone to preoperative chemoradiation therapy followed by surgery.

Preoperative chemoradiation therapy led to an improvement in median survival — 49 months versus 26 months — and a 25 percent higher rate of curative resection compared to surgery alone. Fifteen to 20 percent incremental improvements in survival over three years were also reported. Many of us believe this large, well-conducted randomized trial establishes preoperative chemotherapy and radiation therapy as an acceptable standard.

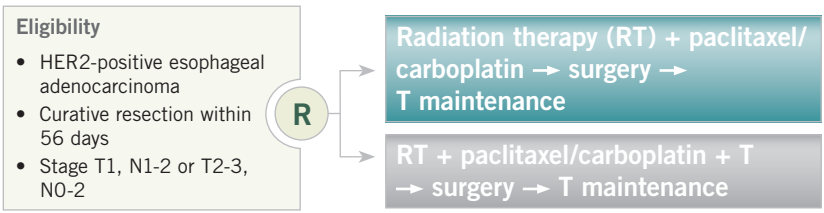
Many upcoming research studies, including an ongoing HER2-directed study in esophageal and GE junction cancers (1.1), are building on this idea to evaluate weekly carboplatin/paclitaxel and radiation therapy as preoperative therapy. Patients with HER2-positive tumors will be randomly assigned to chemotherapy and radiation therapy with or without trastuzumab.

DR LOVE: What is the rationale for the use of trastuzumab?

DR ILSON: In a recently published study of patients with HER2-positive gastric or GE junction cancer who were randomly assigned to receive cisplatin with capecitabine or fluorouracil with or without trastuzumab, the addition of trastuzumab was associated with significant benefits in response rate, progression-free survival and overall survival. A nearly three-month improvement was observed in overall survival (Bang 2010; [1.2]). As a result, the FDA has

1.1 **Phase III Trial of Multimodal Chemotherapy with or without Trastuzumab (T) in Patients with Resectable HER2-Positive Esophageal Adenocarcinoma**

Protocol IDs: RTOG-1010, NCT01196390 **Target Accrual:** 480 (Open)



www.clinicaltrials.gov, July 2011.

approved the use of trastuzumab in HER2-positive GE junction and gastric cancers for first-line treatment of metastatic disease.

DR LOVE: What is the frequency of HER2-positive gastric cancer?

DR ILSON: The rate of HER2-positive tumors is approximately 16 percent for more distal gastric cancer and as high as 20 to 32 percent for proximal GE junction tumors. More diffuse gastric cancers may be positive only six percent of the time compared to the intestinal gastric cancers, which are positive 16 percent of the time (Janjigian 2010). Overall, we expect about a 15 to 20 percent HER2 positivity rate using either FISH or IHC.

1.2

ToGA: Efficacy and Cardiac Events from a Phase III Study of the Addition of Trastuzumab to First-Line Chemotherapy for HER2-Positive Advanced Gastric Cancer

Efficacy	FC (n = 290)	FC + T (n = 294)	Hazard ratio	*p*-value
Overall survival	11.1 mo	13.8 mo	0.74	0.0046
Progression-free survival	5.5 mo	6.7 mo	0.71	0.0002
Overall response rate	35%	47%	—	0.0017
Duration of response	4.8 mo	6.9 mo	0.54	<0.0001

F = fluoropyrimidine; C = cisplatin; T = trastuzumab

Bang YJ et al. *Lancet* 2010;376(9742):687-97.

Tracks 9, 11

DR LOVE: What are some of the latest developments in the treatment of pancreatic cancer?

DR ILSON: Surgery in combination with adjuvant chemotherapy improves survival modestly. We've made improvements using systemic chemotherapy to treat metastatic disease, and the advent of erlotinib improved one-year survival. Most recently, a Phase III trial of combination chemotherapy in pancreatic cancer reported the first survival benefit in nearly 20 years.

This combination, FOLFIRINOX, improved overall survival, more than tripled response rate and almost doubled progression-free survival when compared to gemcitabine alone. One-year survival increased from 20 percent to 48 percent (Conroy 2011; [1.3]).

In the targeted therapy arena, other than erlotinib, drugs like bevacizumab and cetuximab have not yielded any benefit in metastatic disease. We are evaluating a host of new agents — PARP inhibitors and other more specifically targeted agents. The treatment of pancreatic cancer remains a huge challenge, and only a minority of patients are candidates for curative surgery.

DR LOVE: Would you discuss the issue of tolerability and dosing with the FOLFIRINOX regimen?

DR ILSON: I tend to individualize chemotherapy dosing by considering performance status and age. I believe the FOLFIRINOX parent regimen is probably intolerable for elderly patients, so dose adjustments must be made. Alternatively, you can begin with FOLFOX, assess toxicity and add the irinotecan component at cycle two or three if FOLFOX is well tolerated.

Many practitioners believe they have to follow lockstep published chemotherapy protocols, but chemotherapy is not one size fits all, and you can individualize dosing based on the tolerance of your patient.

1.3

Efficacy of FOLFIRINOX versus Gemcitabine in a Phase III Study of Initial Therapy for Stage IV Pancreatic Cancer

	Gemcitabine (n = 171)	FOLFIRINOX (n = 171)	Hazard ratio	*p*-value
ORR	9.4%	31.6%	Not reported	0.001
PFS	3.3 mo	6.4 mo	0.47	<0.001
OS	6.8 mo	11.1 mo	0.57	<0.001

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

Conroy T et al. *N Engl J Med* 2011;364(19):1817-25.

Tracks 10, 12

DR LOVE: What other targeted therapies are under evaluation in pancreatic cancer?

DR ILSON: We are evaluating erlotinib in combination with gemcitabine compared to standard adjuvant gemcitabine alone. The RTOG is sponsoring a randomized national trial. That trial will also open in Europe and is supported through the Intergroup and the SWOG cooperative group (1.4).

It is hoped that this trial will address two questions: (1) Does a targeted agent that seems to work in metastatic disease contribute any benefit in the adjuvant setting? (2) Does the addition of radiation therapy after adjuvant chemotherapy improve outcomes compared to adjuvant chemotherapy alone?

DR LOVE: Outside of a research setting, how do you decide whether to add erlotinib to gemcitabine in metastatic disease?

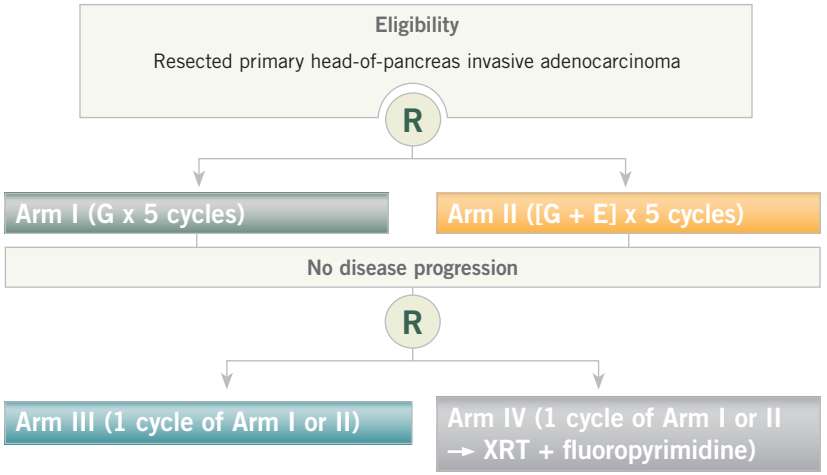
DR ILSON: Before the FOLFIRINOX study, erlotinib was the only drug associated with a survival benefit in metastatic pancreatic cancer. Erlotinib is associated with an increased survival increment of about seven percent. Given the recent data on combination chemotherapy regimens, I begin by using a combination chemotherapy regimen if the patient has a good performance status.

If the patient's disease stabilizes or responds, I may later add erlotinib, given its potential to increase benefit. We know the addition of erlotinib is beneficial in patients who receive gemcitabine monotherapy, but we don't know what it adds to combination treatment in pancreatic cancer. I administer it selectively along with gemcitabine monotherapy and usually add it later so patients aren't subjected to the additional toxicity up front. It is not known if erlotinib is useful in addition to combination therapy, but it is approved for use with gemcitabine-based treatment, so it's a consideration for use in select patients. ■

1.4

Gemcitabine (G) with or without Erlotinib (E) Followed by Chemotherapy with or without Radiation Therapy (XRT) for Patients with Resected Pancreatic Cancer

Protocol IDs: RTOG-0848, CTSU **Target Accrual:** 950 (Open)



NCI Physician Data Query, April 2010; **www.rtog.org**.

SELECT PUBLICATIONS

Bang YJ et al. **Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial.** *Lancet* 2010;376(9742):687-97.

Conroy T et al. **FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.** *N Engl J Med* 2011;364(19):1817-25.

Gaast AV et al. **Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study.** *Proc ASCO* 2010;**Abstract 4004**.

Janjigian YY et al. **HER2 status of patients with gastric cancer (GC) in the United States.** Gastrointestinal Cancers Symposium 2010;**Abstract 30**.

Stahl M et al. **Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction.** *J Clin Oncol* 2009;27(6):851-6.