INTERVIEW

## Peter C Enzinger, MD

Dr Enzinger is Director of the Center for Esophageal and Gastric Cancer and Assistant Professor of Medicine at Harvard Medical School's Dana-Farber Cancer Institute in Boston, Massachusetts.

### Tracks 1-17



## Select Excerpts from the Interview

### Tracks 1, 8

**DR LOVE:** What is your approach to the treatment of advanced gastric and gastroesophageal (GE)-junction cancer?

**DR ENZINGER:** Therapy for gastric cancer continues to be difficult, primarily because the available agents are not very effective. We're still stuck with platinum/5-FU with or without epirubicin. Added to the complexity is whether radiation therapy is of benefit. Radiation oncologists push for radiation therapy extending down the esophagus to the GE junction, even into the proximal stomach. I do believe that radia-

tion therapy can provide additional benefit to patients who are healthy, and platinum agents probably prevent resistance to 5-FU, particularly in terms of lung metastases, but we must find better therapies for these patients. Particularly for patients with HER2-positive disease, trastuzumab and its successors will have a significant impact. I believe we'll see a difference in the near future.

**DR LOVE:** Would you discuss your treatment algorithm for patients with HER2-negative versus HER2-positive gastric or esophageal cancer?

**DR ENZINGER:** I believe at least 3 lines of therapy are active in esophageal or gastric cancer. Platinum/5-FU with or without epirubicin remains front-line treatment, and if the tumor is HER2-positive you would consider adding trastuzumab in place of the epirubicin.

In the second line a taxane-based therapy is appropriate. In patients with significant disease burden or symptoms I recommend a weekly docetaxel/cisplatin/irinotecan combination, which has a high response rate and works well in refractory disease. In patients with lower disease burden who are less symptomatic, weekly single-agent docetaxel or paclitaxel is reasonable. Every 3-week therapy is probably more effective, but it's also more toxic. Finally, if you don't use irinotecan in the second line, that's a third line option by itself or in combination with cisplatin, 5-FU or FOLFIRI.

## Track 4

**DR LOVE:** Getting back to the issue of chemoradiation therapy, would you comment on how this disease is managed in the community and how well the treatment is tolerated?

**DR ENZINGER:** In the past, we used cisplatin/5-FU/radiation therapy for esophageal and GE junction cancer followed by surgery, but it is a toxic regimen. Half of the patients ended up being hospitalized, and the majority of patients were unable to receive the third cycle of cisplatin/5-FU. Some were too weak to proceed to surgery.

**3.1**

### CROSS Study: Neoadjuvant Chemoradiation Therapy (CRT)* for Esophageal or Gastroesophageal-Junction Cancer

| **Efficacy** | **CRT + surgery** (n = 178) | **Surgery alone** (n = 188) | Hazard ratio | *p*-value |
|---|---|---|---|---|
| Median overall survival | 49.4 months | 24.0 months | 0.657 | 0.003 |
| **Adverse events**† | **CRT + surgery** (n = 171) | | **Surgery alone** (n = 186) | |
| Pulmonary complications | 46% | | 44% | |
| Cardiac complications | 21% | | 17% | |
| Chylothorax | 10% | | 6% | |
| Anastomotic leakage | 22% | | 30% | |

* Weekly carboplatin/paclitaxel; † During neoadjuvant CRT and after surgery

The most common major hematologic toxic effects in the CRT + surgery group were leukopenia (6%) and neutropenia (2%); the most common major nonhematologic toxic effects were anorexia (5%) and fatigue (3%).

Van Hagen P et al. *N Engl J Med* 2012;366(22):2074-84.

That brings us to the CROSS study, which was a well-powered trial that reported a survival benefit in both adenocarcinoma and squamous cell carcinoma. Moreover, it used a regimen that most doctors in the community will have no trouble administering — neoadjuvant paclitaxel/carboplatin and radiation therapy (van Hagen 2012; [3.1]). Unlike with cisplatin/5-FU, almost all patients make it through this regimen. Some patients experience fatigue, but we do not see any significant hematologic toxicities. It's a well-tolerated regimen that delivers the patient back to the surgeon intact.

## Track 5

**DR LOVE:** What are your thoughts on the REGARD trial and ramucirumab in advanced gastric or GE junction cancer?

**DR ENZINGER:** The REGARD trial reported a significant improvement in overall survival for patients who received an anti-angiogenesis agent (Fuchs 2013; [3.2]). All of the patients received platinum/5-FU therapy up front and then were randomly assigned to best supportive care or ramucirumab. The results indicated a significant improvement in overall survival and progression-free survival with hardly any toxicity. So in addition to the nearly positive AVAGAST study with bevacizumab in combination with chemotherapy (Ohtsu 2011) and the positive REGARD trial, I believe anti-angiogenesis therapy will play a significant role in this disease in the future.

**3.2**

**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 | 0.047 |
| Median progression-free survival | 2.1 mo | 1.3 mo | 0.483 | <0.0001 |
| Objective response rate | 3% | 3% | — | 0.76 |
| **Select adverse events, Grade ≥3** | **Ramucirumab** (n = 236) | | **Placebo** (n = 115) | |
| Fatigue | 6% | | 10% | |
| Hypertension | 8% | | 3% | |
| Anemia | 6% | | 8% | |

Fuchs CS et al. *Lancet* 2013;S0140-6736(13)61719-5.

## Tracks 14-15

**DR LOVE:** Would you discuss the PRODIGE 4/ACCORD 11 trial data on the use of FOLFIRINOX versus gemcitabine (Conroy 2011; [3.3]) and also the MPACT trial results with *nab* paclitaxel and gemcitabine versus gemcitabine alone (Von Hoff 2013; [3.3]) for metastatic pancreatic cancer?

**DR ENZINGER:** The MPACT study was one of the largest studies ever conducted in this disease, so the survival advantage was statistically significant even though it was only approximately 1.8 months. It was interesting for me to realize that now we have another active agent in this disease. Many of us were using taxanes in the third line,

**3.3**

**Phase III Studies of FOLFIRINOX or *Nab* Paclitaxel (*Nab*-p)/Gemcitabine (Gem) versus Gem Alone in Metastatic Pancreatic Cancer**

| **PRODIGE 4**[1] | Gem | FOLFIRINOX | Hazard ratio | *p*-value |
|---|---|---|---|---|
| ORR | 9.4% | 31.6% | Not reported | <0.001 |
| Median PFS | 3.3 months | 6.4 months | 0.47 | <0.001 |
| Median OS | 6.8 months | 11.1 months | 0.57 | <0.001 |
| **MPACT**[2] | Gem | *Nab*-p/Gem | Hazard ratio | *p*-value |
| ORR* | 7% | 23% | — | $1.1 \times 10^{-10}$ |
| Median PFS* | 3.7 months | 5.5 months | 0.69 | 0.000024 |
| Median OS | 6.7 months | 8.5 months | 0.72 | 0.000015 |

* By independent review

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

[1] Conroy T et al. *N Engl J Med* 2011;364(19):1817-25; [2] Von Hoff DD et al. Gastrointestinal Cancers Symposium 2013;**Abstract LBA148**.

so now the question is, was this simply a large study powered to detect a small difference or is this agent better than a regular taxane? Both studies used gemcitabine as the comparator arm, and toxicity and survival were similar.

We all know not to conduct cross-study comparisons, but if you were to indirectly evaluate *nab* paclitaxel versus FOLFIRINOX by normalizing the 2 arms by creating a ratio, the response rate with *nab* paclitaxel is similar to that with FOLFIRINOX. However, FOLFIRINOX seems to yield better results in terms of survival, with a longer progression-free and overall survival in comparison to gemcitabine/*nab* paclitaxel.

Since the data were presented I've used *nab* paclitaxel in patients with refractory disease and am considering it for those who are not strong enough to receive FOLFIRINOX. Patients who have locally unresectable disease can tolerate this aggressive treatment.

I would also use FOLFIRINOX in patients who we're trying to take to surgery and those who want neoadjuvant therapy but not for those with unresectable metastatic disease. FOLFOX or, alternatively, gemcitabine/*nab* paclitaxel, one followed by the other, is a reasonable compromise for these patients.

In terms of specific toxicities, you observe more neutropenia and febrile neutropenia with FOLFIRINOX. However, patients experience less peripheral neuropathy with FOLFIRINOX although *nab* paclitaxel/gemcitabine causes more fatigue. In practice, I've found anorexia to be a problem with gemcitabine/*nab* paclitaxel. But overall, patients tell me that they prefer gemcitabine/*nab* paclitaxel to FOLFIRINOX. ■

## SELECT PUBLICATIONS


Fuchs CS et al. **Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial.** *Lancet* 2013;S0140-6736(13)61719-5.

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.

Van Hagen P et al. **Preoperative chemoradiotherapy for esophageal or junctional cancer.** *N Engl J Med* 2012;366(22):2074-84.