INTERVIEW

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Tracks 1-12

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Tracks 1-2

DR LOVE: Can you discuss the background and results of ECOG-E3303?

DR LANGER: We conceived of ECOG-E3303 six or seven years ago. Our goal was to evaluate the addition of cetuximab to a standard regimen of chemoradiation therapy including cisplatin for patients with unresectable squamous cell carcinoma of the head and neck (Langer 2008; [1.1]).

During the past 10 to 15 years, chemoradiation therapy had become the standard approach for locally advanced head and neck cancer.

In 2006, Jim Bonner published data demonstrating a survival advantage with cetuximab in combination with radiation therapy compared to radiation therapy alone (Bonner 2006; [3.1, page 13]). Cetuximab is the first targeted agent I'm aware of that's been approved in the setting of definitive radiation therapy. A tremendous appetite exists to try to wed these two approaches by administering both chemoradiation therapy and cetuximab.

Years ago, Dave Adelstein conducted a landmark Phase III trial evaluating radiation therapy alone, full-dose radiation therapy with cisplatin and a split-course radiation therapy with 5-FU/cisplatin. Full-dose radiation therapy with cisplatin had the best outcome (Adelstein 2003). Our intention in ECOG-E3303 was to add cetuximab to that chemoradiation therapy schedule with

1.1

ECOG-E3303: A Phase II Trial of Concurrent Radiation Therapy, Cisplatin and Cetuximab in Unresectable, Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Protocol ID: ECOG-E3303
Accrual: 69 (Closed)

Eligibility

Unresectable, locally advanced SCCHN

ECOG PS 0-1

Treatment

Cetuximab 400 mg/m^2 d1, then 250 mg/m^2 qwk + definitive radiation therapy (70 Gy/2 Gy/d x 7wk) starting d15 + cisplatin 75 mg/m^2 d15, 36 and 57

Efficacy	(n = 60)
Complete response rate	26.7%
Partial response rate	30.0%
Median progression-free survival	15.3 months
Median overall survival (projected)	33.0 months

Select toxicity (≥Grade III)	(n = 66)
Neutropenia	26%
Fatigue	23%
Acneiform rash	26%
Dehydration	20%
Anorexia	37%
Dysphagia	45%
Xerostomia	17%
Mucositis	55%
Nausea/vomiting	21%

SOURCE: Langer CJ et al. *Proc ASCO* 2008;**Abstract 6006**.

a primary endpoint of progression-free survival. We accrued 69 patients, of whom 60 were clearly evaluable (Langer 2008). The demographics of the patients in ECOG-E3303 matched those in Dave Adelstein's trial.

Overall, toxicity in ECOG-E3303 was reasonable, with two Grade V adverse events. We saw a fair amount of mucositis, dysphagia and, of course, acneiform rash. Twenty-six percent of the patients experienced a Grade III rash (Langer 2008; [1.1]).

The response rates don't sound impressive, but we are living in the era of RECIST. I believe RECIST tends to downplay the response status. Overall, the response rate was 57 percent, and the median progression-free survival was 15 months, but that's a fluid endpoint. Our median overall survival was 33 months, and we now have a two-year projected overall survival of 67 percent (Langer 2008; [1.1]).

In Adelstein's study of radiation therapy versus chemoradiation therapy, the three-year overall survival for chemoradiation therapy with cisplatin was 37 percent. These results lend credence to the notion of adding cetuximab to chemoradiation therapy. In fact, RTOG is conducting RTOG-0522, a Phase III trial evaluating full-dose chemoradiation therapy with or without cetuximab (2.1, page 9).

Track 7

DR LOVE: Would you consider radiation therapy in combination with cetuximab in any situations, either with or without chemotherapy?

DR LANGER: Outside of a study, I feel uncomfortable administering all three together. It's still considered an experimental approach. I would certainly offer participation in RTOG-0522 (2.1). If the patient declines — and probably 50 percent of those to whom I've offered it decline — I generally administer a platinum agent alone with radiation therapy. If the patient is not fit enough or another mitigating factor is present, such as age or comorbidity, I substitute cetuximab for cisplatin, which would be identical to Bonner's approach and fits with evidence-based medicine.

Track 8

DR LOVE: What other research questions are being asked related to cetuximab in head and neck cancer?

DR LANGER: Ethan Argiris presented a study at ASCO 2008 that evaluated cetuximab in combination with induction chemotherapy. He omitted 5-FU but continued docetaxel and cisplatin. It was feasible, as we would expect (Argiris 2008). It was a single-arm pilot trial, so we don't have comparative data, but I believe it's a trend we'll see. It won't be docetaxel/cisplatin/5-FU (TPF) alone. It may be TP with cetuximab. We may be using cetuximab to substitute for a less effective, more toxic agent, such as 5-FU.

RTOG-0522 will establish whether cetuximab adds to chemoradiation therapy. Until we have data from that trial, it remains an open question. Paul Harari has completed a Phase II trial in the adjuvant setting, in which cetuximab was administered with radiation therapy and either weekly cisplatin or weekly docetaxel (Harari 2007).

If those data seem promising, I can foresee a trial comparing a platinum agent with radiation therapy to a platinum agent with radiation therapy and cetuximab.

Finally, the EXTREME trial evaluated a platinum agent (carboplatin or cisplatin) and 5-FU with or without cetuximab in patients with recurrent or metastatic disease (Vermorken 2008; [4.1, page 17]).

Again, that trial showed a survival advantage with cetuximab as first-line therapy. I'm not aware of any other disease in which an agent has demonstrated its efficacy so globally, in nearly every setting. ■

SELECT PUBLICATIONS

Adelstein DJ et al. **An Intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer.** *J Clin Oncol* 2003;21(1):92-8. **Abstract**

Argiris AE et al. **Phase II trial of neoadjuvant docetaxel (T), cisplatin (P), and cetuximab (E) followed by concurrent radiation (X), P, and E in locally advanced head and neck cancer (HNC).** *Proc ASCO* 2008;**Abstract 6002**.

Bonner JA et al. **Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.** *N Engl J Med* 2006;354(6):567-78. **Abstract**

Curran D et al. **Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab**. *J Clin Oncol* 2007;25(16):2191-7. **Abstract**

Harari PM et al. **Phase II randomized trial of surgery followed by chemoradiation plus cetuximab for high-risk squamous cell carcinoma of the head and neck (RTOG 0234).** *Proc ASTRO* 2007;**Abstract 22**.

Langer CJ et al. **Preliminary analysis of ECOG 3303: Concurrent radiation (RT), cisplatin (DDP) and cetuximab (C) in unresectable, locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN).** *Proc ASCO* 2008;**Abstract 6006**.

Paccagnella A et al. **Concomitant chemoradiotherapy (CT/RT) vs neoadjuvant chemotherapy with docetaxel/cisplatin/5-fluorouracil (TPF) followed by CT/RT in locally advanced head and neck cancer. Final results of a phase II randomized study.** *Proc ASCO* 2008;**Abstract 6000**.

RTOG 0522: A randomized phase III trial of concurrent accelerated radiation and cisplatin versus concurrent accelerated radiation, cisplatin, and cetuximab [followed by surgery for selected patients] for Stage III and IV head and neck carcinomas. *Clin Adv Hematol Oncol* 2007;5(2):79-81. No abstract available

Vermorken JB et al. **Platinum-based chemotherapy plus cetuximab in head and neck cancer.** *N Engl J Med* 2008;359(11):1116-27. **Abstract**