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Head & Neck Cancer™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

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INTERVIEWS

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CME Certified

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Head and Neck Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Approximately 47,560 new cases of head and neck (H&N) cancer are estimated to occur in the United States during 2008, accounting for three percent of all types of cancer, and more than 11,000 patients will die from the disease. Treatment for patients with H&N cancer is complex and requires a multidisciplinary team of individuals with expertise in the special care needs of these patients. The site and extent of disease and pathologic findings dictate the appropriate surgical approach, radiation field, dose and fractionation and indications for chemotherapy and/or biologic therapy. Published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — practicing medical oncologists and radiation oncologists must be well informed of these advances. To bridge the gap between research and patient care, *Head and Neck Cancer Update* features one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists these physicians with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Recognize the role of HPV in the pathogenesis of oropharyngeal cancer, and describe its impact on patient prognosis and response to treatment.
- Develop evidence-based multimodality treatment approaches for patients with locally advanced and metastatic H&N cancer.
- Assess the impact of radiation therapy with concurrent chemotherapy and/or EGFR inhibition on treatment tolerability and long-term outcomes.
- Appraise the merit of intensity-modulated, image-guided radiation therapy in the treatment of H&N cancer.
- Recommend supportive measures to ameliorate the common toxicities that accompany the local and systemic treatment of H&N cancer.
- Acknowledge the psychosocial, physical and emotional toll associated with the diagnosis and treatment of H&N cancer.
- Delineate the rationale for early-phase clinical trials with novel targeted therapies in H&N cancer, including anti-angiogenic agents and multitargeted kinase inhibitors.
- Counsel appropriately selected patients about participation in ongoing clinical trials.

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INTERVIEW

Corey J Langer, MD

Dr Langer is Professor of Medicine at the University of Pennsylvania and Vice Chair of the Radiation Therapy Oncology Group in Philadelphia, Pennsylvania.

Tracks 1-12

Select Excerpts from the Interview

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**

INTERVIEW

Robert Haddad, MD

Dr Haddad is Clinical Director of the Head and Neck Oncology Program at the Dana-Farber Cancer Institute at Harvard Medical School in Boston, Massachusetts.

Tracks 1-16

Track 1 Prognosis and treatment of human papillomavirus (HPV)-related oropharyngeal cancer

Track 2 Sexual activity and the increasing incidence of HPV-related oropharyngeal cancer

Track 3 Induction cetuximab with docetaxel/cisplatin/5-fluorouracil (C-TPF) in locally advanced H&N cancer

Track 4 Clinical trials combining cetuximab with induction chemotherapy and/or radiation therapy for locally advanced H&N cancer

Track 5 Synergism between cetuximab and chemoradiation therapy

Track 6 Proposed trial of induction chemotherapy evaluating C-TPF with cetuximab/carboplatin/paclitaxel

Track 7 Predictors of response to EGFR monoclonal antibodies in H&N cancer

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Track 12 Clinical trials of the cisplatin/docetaxel/erlotinib triplet in recurrent H&N cancer

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Track 14 Up-front versus delayed placement of percutaneous endoscopic gastrostomy (PEG) feeding tubes during radiation therapy

Track 15 Role of neck dissection after chemoradiation therapy

Track 16 Use of induction chemotherapy to identify candidates for an organ-preservation approach instead of surgical resection

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss the relationship between human papillomavirus (HPV) infection and head and neck cancer?

DR HADDAD: HPV is the cause of the majority of cervical cancer cases. We know, based on recent information, that HPV-16 is also a major cause of oropharyngeal cancer (D'Souza 2007). This is specific for tumors on the

tonsils and tongue base and is not applicable to cancer of the larynx or oral cavity (Gillison 2000). These patients are typically young — in their thirties or early forties — and are nonsmokers or nondrinkers. They present with fairly advanced disease with large lymph node metastases in the neck and large primaries on the tonsil or tongue base. The tumors are highly responsive to chemotherapy and radiation therapy, and the prognosis for these patients with HPV-positive oropharyngeal cancer is much better than for patients with HPV-negative oropharyngeal cancer (Fakhry 2008).

Tracks 3, 6

DR LOVE: Can you review the trial you presented at ASCO 2008 evaluating cetuximab in combination with induction chemotherapy?

DR HADDAD: We evaluated docetaxel, cisplatin and 5-FU (TPF) as induction chemotherapy in combination with cetuximab for patients with locally advanced head and neck cancer (Tishler 2008). It was a Phase I study in which we escalated the dose of 5-FU. We used fixed doses of cisplatin, docetaxel and cetuximab. The dose of 5-FU was escalated from 700 to 850 to 1,000 mg/m^2 per day as a continuous infusion for four days. At a dose of 1,000 mg/m^2 per day, we ran into problems with gastrointestinal toxicity, probably from the 5-FU. So we de-escalated and declared 850 mg/m^2 per day to be the maximum tolerated dose.

We've enrolled only patients with fairly advanced disease, and so far we've had only one failure locally. All of the other patients continue to be in remission and are faring quite well. This was a Phase I/II trial, so at this point we will not draw many conclusions except that the combination is feasible and safe and should be studied further in Phase II and Phase III trials (Tishler 2008).

Track 4

DR LOVE: What do we know about cetuximab in combination with chemoradiation therapy?

DR HADDAD: The study that led to the approval of cetuximab in combination with radiation therapy did not use chemotherapy (Bonner 2006). A remaining question is how to combine cetuximab with concurrent chemoradiation therapy. RTOG is currently performing a large Phase III trial (RTOG-0522) that will enroll more than 700 patients and evaluate chemoradiation therapy with or without cetuximab. The chemotherapy being used in that trial is cisplatin (2.1).

Dr Pfister performed a Phase II study in which cisplatin, radiation therapy and cetuximab were combined, as RTOG is doing now. It was a small study that had to be stopped early because of an unexpected increase in the rate of toxicity. Even with those early toxicities, the overall results showed a promising rate of local control higher than 70 percent and, ultimately, cure for the patients who received these therapies (Pfister 2006).

Unfortunately, I believe a problem occurred with patient selection, and some of the patients enrolled in this trial died of toxicity. So the study was stopped early and could not be completed. The overall data, however, were promising enough for RTOG to consider their current randomized Phase III trial (RTOG-0522).

2.1

Phase III Randomized Study of Chemoradiation Therapy with or without Cetuximab

Protocol IDs: RTOG-0522, NCT00265941
Target Accrual: 720 (Open)

Eligibility

- Stage III or IV squamous cell carcinoma of the oropharynx, hypopharynx or larynx
- No distant metastases
- No prior therapy

R

- Radiation therapy* x 6 weeks + cisplatin days 1 and 22
- Cetuximab weekly (weeks 0 to 7) + radiation therapy* x 6 weeks + cisplatin days 1 and 22

* Radiation therapy = [3D-conformal or IMRT] once or twice a day, five to six days per week

Patients with persistent nodal disease (ie, a residual palpable or radiographic abnormality) undergo neck dissection approximately nine to 10 weeks after completion of treatment.

Study Contact

Radiation Therapy Oncology Group, K Kian Ang, MD, PhD, Tel: 800-392-1611

SOURCE: NCI Physician Data Query, November 2008.

Track 8

DR LOVE: What do you consider reasonable, evidence-based strategies that can be used outside of a protocol setting for patients with locally advanced head and neck cancer?

DR HADDAD: For those patients in whom you perceive a high risk of distant failure — those who have N3, N2b or N2c disease — the options would include sequential therapy with induction chemotherapy followed by concurrent chemoradiation therapy. This is based on the TAX-324 study (Posner 2007; [2.2]). The other option is concurrent chemoradiation therapy with bolus cisplatin administered every three weeks during radiation therapy. That is considered by many to be the standard approach for locally advanced head and neck cancer.

If the patient will not tolerate chemotherapy or refuses chemotherapy, I believe we have enough data to suggest a combination of cetuximab and radiation therapy. For that patient, the combination is superior to radiation therapy

alone, and it does not necessarily increase the toxicity profile apart from the skin reactions (Bonner 2006). ■

2.2

TAX-324: Induction Cisplatin and 5-FU Alone (PF) or with Docetaxel (TPF) Followed by Chemoradiation Therapy in Patients with Locally Advanced Head and Neck Cancer

Parameter	TPF (n = 255)	PF (n = 246)	HR (95% CI)	*p*-value
Overall survival (months)	71	30	0.70 (0.54-0.90)	0.006
Two-year	67%	55%		
Three-year	62%	48%		
Progression-free survival (months)	36	13	0.71 (0.56-0.90)	0.004
Two-year	53%	42%		
Three-year	49%	37%		
Time to progression (months)	NR	14	0.66 (0.50-0.86)	0.002
Two-year	57%	43%		
Three-year	54%	40%		
Treatment failure	35%	45%	0.70 (0.53-0.92)	0.01
Locoregional	30%	38%	0.73 (0.54-0.99)	0.04
Distant	5%	9%	0.60 (0.30-1.18)	0.14
Second primary	4%	4%		

HR = hazard ratio; CI = confidence interval; NR = not reached

SOURCE: Posner MR et al. *N Engl J Med* 2007;357(17):1705-15. **Abstract**

SELECT PUBLICATIONS

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**

D'Souza G et al. **Case-control study of human papillomavirus and oropharyngeal cancer.** *N Engl J Med* 2007;356(19):1944-56. **Abstract**

Fakhry C et al. **Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial.** *J Natl Cancer Inst* 2008;100(4):261-9. **Abstract**

Gillison ML et al. **Evidence for a causal association between human papillomavirus and a subset of head and neck cancers.** *J Natl Cancer Inst* 2000;92(9):709-20. **Abstract**

Pfister DG et al. **Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: A pilot phase II study of a new combined-modality paradigm.** *J Clin Oncol* 2006;24(7):1072-8. **Abstract**

Posner MR et al; TAX 324 Study Group. **Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer.** *N Engl J Med* 2007;357(17):1705-15. **Abstract**

Tishler RB et al. **Cetuximab added to docetaxel, cisplatin, 5-fluorouracil induction chemotherapy (C-TPF) in patients with newly diagnosed locally advanced head and neck cancer: A phase I study.** *Proc ASCO* 2008;**Abstract 6001**.

Wanebo HJ et al. **Phase II evaluation of cetuximab (C225) combined with induction paclitaxel and carboplatin followed by C225, paclitaxel, carboplatin, and radiation for stage III/IV operable squamous cancer of the head and neck (ECOG, E2303).** *Proc ASCO* 2007;**Abstract 6015**.

INTERVIEW

David I Rosenthal, MD

Dr Rosenthal is Professor, Director of Head and Neck Translational Research and Acting Section Chief of the Head and Neck Section in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-11

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss the findings from RTOG-0129, comparing conventional versus accelerated radiation therapy and concurrent cisplatin for patients with Stage III or IV squamous cell carcinoma of the head and neck?

DR ROSENTHAL: In this trial, all the patients received cisplatin, and they were randomly assigned to receive either standard fractionation — five fractions a week for seven weeks for a total dose of 70 Gray — or concomitant boost treatment, which delivers approximately the same total dose, 72 Gray, in six weeks (Ang 2007). The question is whether, in the setting of concurrent chemotherapy, it is advantageous to accelerate the radiation therapy.

The study closed three years ago, and the data are now maturing. We hope to have efficacy data in time for ASCO 2009. The preliminary safety data suggested that while some increase in mucositis and earlier acute toxicities occurred, the risk of some of the more worrisome consequential toxicities, such as dysphagia and longer-term feeding-tube dependency, is not increased (Ang 2007).

A study from Germany several years ago asked a similar question, but in that study all of the patients received accelerated fractionated radiation therapy and were randomly assigned to receive chemotherapy or not (Staar 2001). No improvement in survival outcomes occurred for the group that received both therapies, and almost half of the two-year survivors on that arm were feeding-tube dependent.

Therefore, I believe we need to be careful in using these aggressive chemoradiation therapy regimens until we have a clear signal of safety and efficacy. In my practice, I prefer to use concurrent chemotherapy with once daily radiation therapy until we see an advantage in accelerating radiation therapy.

Track 8

DR LOVE: What's your take on the role of cetuximab in the treatment of head and neck cancer?

DR ROSENTHAL: The improvement in locoregional control and survival with cetuximab when combined with radiation therapy (Bonner 2006; [3.1]) is similar to the data seen when combining cytotoxic chemotherapy and radiation therapy. Remarkably, the data for cetuximab in combination with radiation therapy showed no increase in mucositis, feeding-tube requirements or Grade III dysphagia (Bonner 2006; [3.2]).

The main scenario where I consider this agent off study now is for patients who are ineligible for cisplatin as a radiation sensitizer. Another involves the patient with a more borderline tumor, in which the physician may feel uncomfortable using radiation therapy alone but is hesitant to add the toxicities of concurrent chemotherapy.

Much debate has taken place regarding how we might use cetuximab instead of chemotherapy. We don't have data directly comparing cetuximab to cisplatin as a radiation sensitizer. The results of the study comparing cetuximab with radiation therapy to radiation therapy alone (Bonner 2006; [3.1]) seem to be as good as the data from the trials in which chemotherapy was used.

DR LOVE: Is there any situation in which you would use the combination of cetuximab, chemotherapy and radiation therapy in clinical practice?

DR ROSENTHAL: I don't recommend it, and labeling specifically recommends that it not be used. We typically don't do it, even in our academic setting, where sometimes we use more aggressive therapies.

One published study combined accelerated radiation therapy, chemotherapy and cetuximab, and it closed early due to untoward toxicities. However, positive outcomes were observed with the combination, and some of the toxicities probably could have been prevented had we known about some of the electrolyte-wasting properties, such as hypomagnesemia (Pfister 2006). Ultimately we might use this strategy, but I believe we need to wait for trials to validate its safety and efficacy.

3.1

Phase III Randomized Trial of High-Dose Radiation Therapy with or without Cetuximab for Patients with Locoregionally Advanced Squamous Cell Head and Neck Cancer: Efficacy Data

Protocol IDs: UAB-9901, NCT00004227
Accrual: 424 (Closed)

Eligibility
- Stage III or IV squamous cell carcinoma of the oropharynx, hypopharynx or larynx
- No distant metastases
- No prior therapy

R

- High-dose radiation therapy x 7 to 8 weeks
- High-dose radiation therapy x 7 to 8 weeks + cetuximab weekly during radiation therapy

	Radiation therapy and cetuximab (n = 211)	Radiation therapy alone (n = 213)	Hazard ratio (95% CI)	*p*-value*
Median duration of locoregional control	24.4 months	14.9 months	0.68 (0.52-0.89)	0.005
Median progression-free survival	17.1 months	12.4 months	0.70 (0.54-0.90)	0.006
Median overall survival	49.0 months	29.3 months	0.74 (0.57-0.97)	0.03

* Log-rank test; CI = confidence interval

SOURCE: Bonner JA et al. *N Engl J Med* 2006;354(6):567-78. **Abstract**

Track 10

DR LOVE: What about the role of induction chemotherapy?

DR ROSENTHAL: Induction chemotherapy took hold after data from The Department of Veterans Affairs Laryngeal Cancer Study Group suggested it had a clear role in organ preservation (The Department of Veterans Affairs Laryngeal Cancer Study Group 1991). Subsequent trials then showed that despite an improvement in response, even complete response, it did not ultimately affect locoregional control or survival.

Recently we have seen trials evaluating more active drugs and combinations in the induction setting. Two Phase III trials — TAX-323 and TAX-324 — evaluated cisplatin/5-FU with or without docetaxel in patients who were to receive radiation therapy. Both trials reported improved survival with the addition of docetaxel (Vermorken 2007; Posner 2007; [2.2, page 10]). ■

3.2

Radiation Therapy with Cetuximab for Squamous Cell Head and Neck Cancer

"An exceptional feature of this randomized, phase 3 trial, which was carried out among patients with head and neck cancer who were treated with curative intent, was the finding of a survival advantage associated with the use of a molecular targeting agent, cetuximab, delivered in conjunction with radiation.

We found that the addition of cetuximab to high-dose radiotherapy significantly increased both the duration of control of locoregional disease and survival among patients with locoregionally advanced head and neck cancer.

With the exception of acneiform rash and infusion-related events, the incidence rates of severe (grades 3, 4, and 5) reactions were similar in the two treatment groups. Notably, cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, dysphagia, pain, weight loss, and performance-status deterioration."

SOURCE: Bonner JA et al. *N Engl J Med* 2006;354(6):567-78. **Abstract**

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Ang K et al. **A Phase III trial to compare standard versus accelerated fractionation in combination with concurrent cisplatin for head and neck carcinomas (RTOG 0129): Report of compliance and toxicity.** *Proc ASTRO* 2007;**Abstract 21**.

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**

The Department of Veterans Affairs Laryngeal Cancer Study Group. **Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer.** *N Engl J Med* 1991;324(24):1685-90. **Abstract**

Jensen AD et al. **Treatment of non-small cell lung cancer with intensity-modulated radiation therapy in combination with cetuximab: The NEAR protocol (NCT00115518).** *BMC Cancer* 2006;6:122. **Abstract**

Pfister DG et al. **Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: A pilot phase II study of a new combined-modality paradigm.** *J Clin Oncol* 2006;24(7):1072-8. **Abstract**

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INTERVIEW

Everett E Vokes, MD

Dr Vokes is Director of the Section of Hematology/Oncology, Vice-Chairman for Clinical Research in the Department of Medicine, Deputy Director at the Cancer Research Center and John E Ultmann Professor of Medicine and Radiation and Cellular Oncology at The University of Chicago in Chicago, Illinois.

Tracks 1-10

Track 1	Role of chemoradiation therapy in the treatment of H&N cancer
Track 2	Approaches to reduce the long-term side effects of chemoradiation therapy for H&N cancer
Track 3	Concurrent chemoradiation therapy with or without induction chemotherapy in Stage III/IV H&N cancer
Track 4	Clinical trial strategies to incorporate cetuximab into chemoradiation therapy in Stage III/IV H&N cancer
Track 5	Selection of patients for clinical therapy incorporating cetuximab with radiation therapy or chemotherapy in H&N cancer
Track 6	Therapeutic algorithm for locally advanced H&N cancer
Track 7	Behavioral counseling and supportive care to ameliorate toxicity from chemoradiation therapy
Track 8	Translating experience with anti-angiogenic agents in NSCLC to investigations in H&N cancer
Track 9	Potential clinical implications of HPV status in H&N cancer
Track 10	Frequently asked questions by medical oncologists about H&N cancer treatment

Select Excerpts from the Interview

Track 3

DR LOVE: What are some of the major Phase III clinical trials that you believe will shape the treatment of head and neck cancer in the next few years?

DR VOKES: The largest question in our minds at the University of Chicago is that of the competing successful models — induction chemotherapy, concurrent chemoradiation therapy and concurrent targeted therapy and radiation therapy. Induction chemotherapy with the addition of docetaxel to platinum/5-FU has been shown to be superior to platinum/5-FU alone (Posner 2007; [2.2]). Induction chemotherapy, hence, has a role in the combined-modality, curative-intent setting. Concomitant chemoradiation therapy is superior to radiation therapy alone (Bourhis 2004), so that has a

role. Recent evidence suggests that the addition of cetuximab to radiation therapy also increases efficacy (Bonner 2006; [3.1]).

If you consider what these approaches do, differentially, you can postulate ways to combine them quite rationally. Concurrent chemoradiation, for example, will lead to better local control but not necessarily to better systemic control. Induction chemotherapy, on the other hand, I believe largely addresses micrometastatic systemic disease.

Hence, several randomized trials are underway. One trial (NCT00117572), which we are leading with Ezra Cohen as the principal investigator, is evaluating whether two cycles of induction chemotherapy administered before concurrent chemoradiation therapy can add further benefit compared to chemoradiation therapy alone. Marshall Posner and his group are leading a similar trial, and a European trial is also underway.

Track 5

DR LOVE: In which situations, if any, do you integrate cetuximab into the treatment for patients not enrolled in a study?

DR VOKES: The addition of cetuximab to radiation therapy off protocol is attractive because it is well tolerated and acts as a radiation sensitizer. We would consider using cetuximab with radiation therapy for somewhat older patients who may be frail and have comorbidities such that we would be reluctant to administer chemotherapy. Similarly, we might consider cetuximab with radiation therapy for patients with Stage III disease who were similar to the patients included in the trial published by Bonner (Bonner 2006; [3.1, page 13]) — those who may be overtreated if they received induction chemotherapy or one of the heavier chemoradiation therapy regimens.

DR LOVE: Does cetuximab have a role in recurrent or metastatic disease?

DR VOKES: For a patient with unresectable recurrent disease or metastatic disease, chemotherapy has been the standard for many years. Repeated trials have compared agents or one combination to another.

We never had a trial positive for survival until the EXTREME trial, which evaluated a platinum agent (cisplatin or carboplatin) and 5-FU with or without cetuximab (Vermorken 2008; [4.1]). Investigators reported an approximate two-month gain in overall and progression-free survival with the addition of cetuximab to chemotherapy. This was the first trial during my career as a head and neck oncologist that improved survival in the recurrent disease setting. So first-line chemotherapy for recurrent or metastatic disease, I believe, should include cetuximab.

Track 6

DR LOVE: How do you approach treatment for patients with locally advanced disease off study?

DR VOKES: Our first goal for that group of patients is cure, and a second goal is organ preservation. Off protocol and based on many years of prospective trials, we offer aggressive concurrent chemoradiation therapy as our first approach. The regimen we use is quite intensive and involves administering paclitaxel, infusional 5-FU and oral hydroxyurea with twice-daily radiation therapy. Chemoradiation therapy is administered every other week for five cycles for a total radiation dose of 75 Gray. Without adding induction chemotherapy, we have reported long-term cure rates in the 60 to 70 percent range in this group of patients with this regimen (Rosen 2003; Kies 2001).

DR LOVE: What about the role of induction chemotherapy off study?

DR VOKES: I believe induction chemotherapy is conceptually attractive when patients have advanced nodal disease. If the tumor has spread from the primary and ipsilateral nodes, multiple lymph nodes are involved or there are bilateral lymph nodes and an N3 node, we would worry greatly about that as a predictor of widespread systemic micrometastatic disease. For that group of patients I would think long and hard about using induction chemotherapy because I believe they might benefit from systemic exposure to chemotherapy. However, in a strictly scientific sense, that remains to be proven. ■

4.1

EXTREME Trial: A Phase III Randomized Study of Platinum/5-FU with or without Cetuximab as First-Line Therapy for Recurrent or Metastatic SCCHN

	Cetuximab + platinum/5-FU (n = 222)	Platinum/5-FU (n = 220)	HR (95% CI)	*p*-value (log-rank)
Median overall survival	10.1 months	7.4 months	0.80 (0.64-0.99)	0.04
Median progression-free survival	5.6 months	3.3 months	0.54 (0.43-0.67)	<0.001
Time to treatment failure	4.8 months	3.0 months	0.59 (0.48-0.73)	<0.001

SOURCE: Vermorken JB et al. *N Engl J Med* 2008;359(11):1116-27. **Abstract**

SELECT PUBLICATIONS

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**

Bourhis J et al. **Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemoradiotherapy.** *Proc ASCO* 2004;**Abstract 5505**.

Kies MS et al. **Concomitant infusional paclitaxel and fluorouracil, oral hydroxyurea, and hyperfractionated radiation for locally advanced squamous head and neck cancer.** *J Clin Oncol* 2001;19(7):1961-9. **Abstract**

Posner MR et al; TAX 324 Study Group. **Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer.** *N Engl J Med* 2007;357(17):1705-15. **Abstract**

Rosen FR et al. **Multicenter randomized Phase II study of paclitaxel (1-hour infusion), fluorouracil, hydroxyurea, and concomitant twice daily radiation with or without erythropoietin for advanced head and neck cancer.** *Clin Cancer Res* 2003;9(5):1689-97. **Abstract**

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The projected median overall survival in ECOG-E3033 with concurrent radiation therapy, cisplatin and cetuximab for unresectable, locally advanced SCCHN is _____.**
   a. 15 months
   b. 33 months
   c. 45 months

2. **Approximately _____ of patients in the ECOG-E3303 trial experience Grade III or IV rash after concurrent radiation therapy, cisplatin and cetuximab.**
   a. Three percent
   b. 13 percent
   c. 26 percent

3. **HPV infection has been associated with cancer of the _____.**
   a. Tonsils
   b. Tongue base
   c. Larynx
   d. Both a and b
   e. All of the above

4. **The prognosis for patients with HPV-positive oropharyngeal cancer is better than for patients with HPV-negative oropharyngeal cancer.**
   a. True
   b. False

5. **Cetuximab is currently indicated in combination with _____ for patients with head and neck cancer.**
   a. Chemotherapy
   b. Radiation therapy
   c. Chemoradiation therapy
   d. All of the above

6. **RTOG-0522 is a Phase III trial evaluating chemoradiation therapy with or without _____ for patients with Stage III/IV head and neck cancer.**
   a. Vandetanib
   b. Cetuximab
   c. Panitumumab
   d. Bevacizumab

7. **In a Phase I trial, the maximum tolerated dose of 5-FU in combination with cisplatin, docetaxel and cetuximab was _____ mg/m^2 per day as a continuous infusion for four days.**
   a. 700
   b. 850
   c. 1,000
   d. None of the above

8. **Induction therapy with docetaxel/cisplatin/5-FU is superior to induction therapy with cisplatin/5-FU for patients with locally advanced head and neck cancer.**
   a. True
   b. False

9. **For patients with locally advanced squamous cell head and neck cancer, a Phase III randomized trial demonstrated that cetuximab with radiation therapy was _____ to radiation therapy alone.**
   a. Comparable
   b. Superior
   c. Inferior

10. **In the EXTREME study, patients with previously untreated recurrent or metastatic head and neck cancer who received a three-drug combination of _____ had a better overall survival than those who were treated with a two-drug combination.**
    a. Docetaxel/platinum/5-FU
    b. Cetuximab/platinum/5-FU
    c. Both a and b
    d. None of the above

11. **In both Phase III trials TAX-323 and TAX-324, evaluating cisplatin/5-FU with or without docetaxel as induction therapy for patients with unresectable squamous cell carcinoma of the head and neck, the addition of docetaxel _____ improve survival.**
    a. Did
    b. Did not

Post-test answer key: 1b, 2c, 3d, 4a, 5b, 6b, 7b, 8a, 9b, 10b, 11a

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Head and Neck Cancer Update — Issue 1, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Role of HPV in the etiology of oropharyngeal cancer and its impact on prognosis and response to treatment 4 3 2 1
- Cetuximab with induction chemotherapy or concurrent with radiation therapy for locally advanced H&N cancer 4 3 2 1
- Agents and radiation therapy techniques for amelioration of treatment-induced mucositis and xerostomia 4 3 2 1
- Rationale for the up-front and delayed placement of percutaneous endoscopic gastrostomy feeding tubes 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Role of HPV in the etiology of oropharyngeal cancer and its impact on prognosis and response to treatment 4 3 2 1
- Cetuximab with induction chemotherapy or concurrent with radiation therapy for locally advanced H&N cancer 4 3 2 1
- Agents and radiation therapy techniques for amelioration of treatment-induced mucositis and xerostomia 4 3 2 1
- Rationale for the up-front and delayed placement of percutaneous endoscopic gastrostomy feeding tubes 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: . . . . . .

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: . . . . . .

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: . . . . . .

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Recognize the role of HPV in the pathogenesis of oropharyngeal cancer, and describe its impact on patient prognosis and response to treatment. . . . . 4 3 2 1 N/M N/A
- Develop evidence-based multimodality treatment approaches for patients with locally advanced and metastatic H&N cancer. . . . . 4 3 2 1 N/M N/A
- Assess the impact of radiation therapy with concurrent chemotherapy and/or EGFR inhibition on treatment tolerability and long-term outcomes. . . . . 4 3 2 1 N/M N/A
- Appraise the merit of intensity-modulated, image-guided radiation therapy in the treatment of H&N cancer. . . . . 4 3 2 1 N/M N/A
- Recommend supportive measures to ameliorate the common toxicities that accompany the local and systemic treatment of H&N cancer. . . . . 4 3 2 1 N/M N/A
- Acknowledge the psychosocial, physical and emotional toll associated with the diagnosis and treatment of H&N cancer. . . . . 4 3 2 1 N/M N/A
- Delineate the rationale for early-phase clinical trials with novel targeted therapies in H&N cancer, including anti-angiogenic agents and multitargeted kinase inhibitors. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about participation in ongoing clinical trials. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

. . . . . .

What additional information or training do you need on the activity topics or other oncology-related topics?

. . . . . .

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

Additional comments about this activity:

.....

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As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

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4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Corey J Langer, MD	4 3 2 1	4 3 2 1
Robert Haddad, MD	4 3 2 1	4 3 2 1
David I Rosenthal, MD	4 3 2 1	4 3 2 1
Everett E Vokes, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

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