INTERVIEW

Everett E Vokes, MD

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Tracks 1-10

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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
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Track 7	Behavioral counseling and supportive care to ameliorate toxicity from chemoradiation therapy
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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**