HNCU | 2007 VOL 1 | ISSUE 1

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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LAUNCH ISSUE

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Head and Neck Cancer Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Existing and emerging multimodality treatment regimens utilized in the routine management of head and neck cancers necessitate the physician's working knowledge of novel surgical, radiation and chemotherapeutic techniques. Ongoing clinical trials will continue to refine the optimal management of these tumors, and the introduction of innovative targeted compounds may offer individualized treatment options that offer increased efficacy and improved tolerability. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, *Head and Neck Cancer Update* will utilize one-on-one conversations with leading oncology investigators discussing the interdisciplinary management of head and neck cancers. By providing access to the latest research developments and expert perspectives on the disease, this CME program will assist medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the implications of emerging clinical trial data on the treatment of head and neck cancer, and incorporate these data into management strategies in the local, locally advanced, recurrent and metastatic disease settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Review the contributing etiologic factors relevant to the development of head and neck tumors, and explain how they impact patient-specific prognosis and treatment decisions.
- Describe and implement an algorithm for the multidisciplinary management of head and neck cancer, integrating the roles of the practicing head and neck surgeon, radiation oncologist, medical oncologist and other healthcare professionals delivering necessary ancillary care and support.
- Review the existing and evolving clinical trial data demonstrating the benefit and safety of EGFR-directed single-agent and combined therapy in the front-line and progressive-disease settings, and explain how this molecular pathway impacts tumorigenesis.
- Discuss adverse effects associated with the treatment of head and neck cancer and their impact on selection of therapy and patient quality of life.
- Identify consensus-based acute and prophylactic strategies to manage dermatotoxicities associated with the clinical use of EGFR inhibitors.
- Describe the psychosocial implications of harboring a tumor of the head or neck and offer strategies to improve long-term physical outcomes and assist patients with disease coping.

PURPOSE OF THIS ISSUE OF *HEAD AND NECK CANCER UPDATE*

The purpose of Issue 1 of *Head and Neck Cancer Update* is to support these global objectives by offering the perspectives of Drs Kim, Posner and Curran on the integration of emerging clinical research data into the management of head and neck cancer.

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This program is supported by educational grants from ImClone Systems and Sanofi-Aventis.

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INTERVIEW

Edward S Kim, MD

Dr Kim is Assistant Professor of Medicine in the Department of Thoracic, Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-20

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss the emerging role of cetuximab in head and neck cancer?

DR KIM: In preclinical models, cetuximab seemed very synergistic with radiation therapy.

That led to a series of experiments and small trials, which culminated with Dr Bonner's report published in *The New England Journal of Medicine* (Bonner 2006).

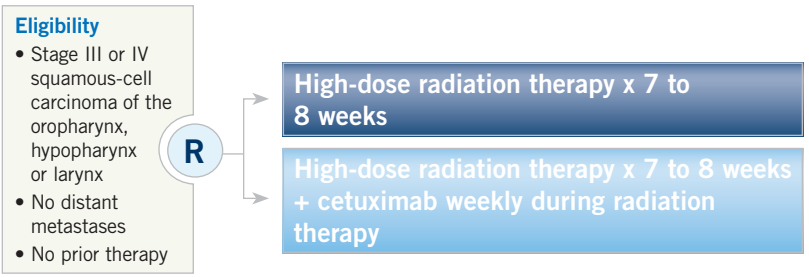
In that trial, the investigators evaluated cetuximab with radiation therapy versus radiation therapy alone for patients with locally advanced squamous-cell head and neck cancer. They demonstrated superiority with cetuximab (1.1).

The bonus was that, other than rash and hypersensitivity reactions, cetuximab added no toxicities to radiation therapy (Bonner 2006; [3.1, page 18]).

1.1

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

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



Efficacy Results at a Median Follow-Up of 54 Months

	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**

Tracks 3, 12

DR LOVE: In a clinical setting, in which situations are you using cetuximab for locally advanced disease?

DR KIM: We tend to use cetuximab for patients who have minimal-bulk disease — N1 disease of the oropharynx because the oropharynx hosts a highly radiosensitive tumor — and for patients whom we don't want to treat with high-dose cisplatin.

For patients who require chemoradiation therapy (ie, those with bulky neck nodes or primary tumors in unfavorable locations such as the hypopharynx or base of the tongue), concurrent chemoradiation therapy with high-dose cisplatin is still the answer.

RTOG-0522 is trying to determine whether cisplatin/cetuximab in combination with radiation therapy is better than radiation therapy and cisplatin (1.2).

DR LOVE: What information do we have about chemoradiation therapy with cetuximab, in terms of safety?

DR KIM: Safety with cetuximab has been good. You don't see exacerbations of mucositis.

Clearly we don't have any myelosuppression, which is one of the big issues with cisplatin and results in many patients having to delay their chemotherapy. We try to plan three doses over a seven-week period, but frequently patients can receive only two doses.

1.2

Phase III Randomized Study of Concurrent Cisplatin/Radiation Therapy with or without Cetuximab for Patients with Stage III or IV Squamous-Cell Head and Neck Cancer

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 2007.

The beauty of a drug like cetuximab is that you don't have these side effects — it's only the rash, and you're using only eight doses, so the rash will go away. If you present that as a possible alternative treatment, then patients are amenable to it.

DR LOVE: Is it your take that cetuximab doesn't exacerbate the toxicities associated with radiation therapy?

DR KIM: Absolutely. Many of us were worried that the rash might become a problem in the radiated field especially.

What's ironic, as we've observed, is that patients who have undergone radiation therapy to an area and then receive cetuximab do not develop a rash in the radiated area.

DR LOVE: What's your impression in terms of quality of life in patients treated with radiation therapy and cetuximab?

DR KIM: As long as the rash is managed correctly and it's not too severe, and as long as patients don't have a hypersensitivity reaction — which they can have with taxanes and other drugs — they tolerate cetuximab beautifully. Cetuximab is easy to administer. It is administered weekly, but patients don't mind.

Tracks 5-6

DR LOVE: Can you discuss the TAX-323 clinical trial results?

DR KIM: The study used four cycles of induction TPF (docetaxel/cisplatin/5-FU) followed by radiation therapy alone. The data for TPF were compelling when compared to PF (cisplatin/5-FU). We learned that TPF, without the expense of toxicities, was better than PF (Remenar 2006; [2.2, page 13]).

In the US, we don't generally like to use four cycles of induction therapy. Three cycles are adequate, and we don't want to delay the curative therapy, which is radiation therapy, much longer than that.

DR LOVE: Which regimen do you use as induction therapy?

DR KIM: We know that PF, which was the historical standard, is inferior to TPF without any tradeoff in side effects (Remenar 2006; Posner 2007).

You're not increasing side effects by adding docetaxel. Sometimes an occasional patient is unable to tolerate TPF. When I use TPF, I administer three cycles with growth factors.

I treat patients with two cycles and then restage the disease to make sure the tumor is shrinking. The patient knows before anybody else because TPF works well.

You can see the tumors shrink, which attests to the fact that squamous-cell tumors of the head and neck are particularly chemosensitive. After completing the third round of chemotherapy, I send the patient back to radiation therapy.

For patients with a poor cardiac status, multiple comorbidities or poor kidney function in whom we would like to start with induction therapy, we sometimes substitute carboplatin for cisplatin and drop the 5-FU.

Again, we have no data to support such a strategy. Many of us wondered whether cisplatin/docetaxel was as good as platinum/docetaxel/5-FU, but such a study hasn't been and probably won't ever be conducted.

For a fit patient, many times in the past, oncologists would pick a regimen such as platinum/5-FU or carboplatin/paclitaxel. Clearly we have a better regimen now, which is TPF. So if you decide to use induction therapy and the patient can tolerate it, TPF is the regimen you should use these days.

DR LOVE: With TPF, how much of a problem is febrile neutropenia if you use growth factors?

DR KIM: When I use growth factors, I don't see too much febrile neutropenia. Most of the side effects I've seen from TPF are based on 5-FU. Patients will describe mucositis or hand-foot syndrome. Those types of toxicities have compelled me to either hold 5-FU or decrease the dose. Generally, however, if patients are faring well and you can keep their blood counts up, they tolerate the regimen decently.

Track 15

DR LOVE: Can you talk about the design and findings of the EXTREME trial? How do you incorporate those results into your practice?

DR KIM: The EXTREME study (Vermorken 2007a; [1.3]) was a nice proof-of-principle study, which validated EGFR-directed therapy even more firmly than the Bonner study (Bonner 2006). Why do I say that?

When we talked about the Bonner study, we knew that radiosensitization worked with chemotherapy. We now also know that it works with EGFR-directed therapy. What we didn't know was whether you could combine a drug that targets EGFR with chemotherapy and obtain a benefit.

Prior studies in recurrent metastatic head and neck cancer demonstrated that two drugs were no better than one drug. Dr Forastiere and Dr Jacobs have reported Intergroup and SWOG data to suggest that (Forastiere 1992; Jacobs 1992). So some people felt that methotrexate was a valid single-agent option in recurrent, metastatic disease.

Based on the old studies, that could not be disputed. Now, for the first time, we have proof that three drugs — a platinum/5-FU/cetuximab — are better than two drugs. We've never observed that before.

The addition of cetuximab did not seem to exacerbate side effects, and overall survival was improved by almost three months (Vermorken 2007a; [1.3]). I assume that cetuximab will now be incorporated into the first-line setting for recurrent, metastatic head and neck cancer.

1.3

Efficacy and Safety in 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	Platinum/5-FU	HR (95% CI)	*p*-value
Median overall survival (months)	10.1	7.4	0.797 (0.644-0.986)	0.0362
Grade III/IV adverse events	33.6%	32.0%	—	—

SOURCE: Vermorken J et al. Presentation. ASCO 2007a;**Abstract 6091**.

Track 19

DR LOVE: You coauthored a fascinating paper, with Tom Lynch and Mario Lacouture, examining the issue of EGFR inhibitors and cutaneous toxicity (Lynch 2007). Could you summarize some of your conclusions?

DR KIM: To me, it is such a shame when a patient has to have a therapy stopped or held due to a rash.

With patients who develop neutropenic fever, you obtain cultures and administer antibiotics. Then they come back and you treat them with the next dose of chemotherapy.

We have a patient who develops a rash, and we say, "We're not going to use the drug any more." I believe that's a situation that can be avoided.

It requires a proactive approach from both the patient and the medical team to try to avoid the rash (1.4). The strategies we've developed at MD Anderson are similar to those Mario has developed.

1.4

Preventive Measures for the Skin Toxicities Associated with EGFR Inhibitors (EGFRI)

"On initiation of EGFRI therapy, patients should be advised to moisturize dry areas of the body twice a day.

For this purpose, a thick alcohol-free emollient is recommended. Patients should also be advised to minimize their exposure to sunlight, as rash may be more severe in areas of skin that are exposed to sunlight (ie, the face and upper chest). The use of a broad-spectrum sunscreen with a sun protection factor of 15 or higher is therefore recommended.

Physical sunscreens (containing zinc oxide or titanium dioxide) are preferred over chemical sunscreens, should be applied 1–2 hours prior to sun exposure, and repeated if exposure is prolonged."

SOURCE: Lynch TJ Jr et al. *Oncologist* 2007;12(5):610-21. **Abstract**

It's about being proactive — not simply throwing creams on people and hoping the rash will go away. We want to move quickly to systemic therapies — antibiotics and/or steroids — to try to avoid any of these Grade III toxicities (1.4). ■

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**

Bonner JA et al. **The relationship of cetuximab-induced rash and survival in patients with head and neck cancer treated with radiotherapy and cetuximab.** *Proc ASTRO* 2005;**Abstract 2005**.

Calais G et al. **Randomized phase III trial comparing induction chemotherapy using cisplatin (P) fluorouracil (F) with or without docetaxel (T) for organ preservation in hypopharynx and larynx cancer. Preliminary results of GORTEC 2000-01.** *Proc ASCO* 2006;**Abstract 5506**.

Cooper JS et al. **Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck.** *N Engl J Med* 2004;350(19):1937-44. **Abstract**

Forastiere AA et al. **Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil vs methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Group study.** *J Clin Oncol* 1992;10(8):1245-51. **Abstract**

Jacobs C et al. **A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck.** *J Clin Oncol* 1992;10(2):257-63. **Abstract**

Kim ES et al. **Final results of a phase II study of erlotinib, docetaxel and cisplatin in patients with recurrent/metastatic head and neck cancer.** *Proc ASCO* 2007;**Abstract 6013**.

Lynch TJ Jr et al. **Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: An evolving paradigm in clinical management**. *Oncologist* 2007;12(5):610-21. **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**

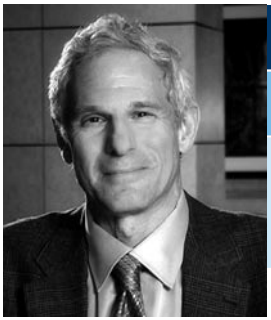
Remenar E et al. **A randomized phase III multicenter trial of neoadjuvant docetaxel plus cisplatin and 5-fluorouracil (TPF) versus neoadjuvant PF in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN). Final analysis of EORTC 24971 [TAX 323].** *Proc ASCO* 2006;**Abstract 5516**.

Salama JK et al. **Chemoradiotherapy for locally advanced head and neck cancer.** *J Clin Oncol* 2007;25(26):4118-26. **Abstract**

Saltz L et al. **The presence and intensity of the cetuximab-induced acne-like rash predicts increased survival in studies across multiple malignancies.** *Proc ASCO* 2003;**Abstract 817**.

Vermorken J et al. **Cetuximab extends survival of patients with recurrent or metastatic SCCHN when added to first line platinum based therapy — Results of a randomized phase III (Extreme) study.** *Proc ASCO* 2007a;**Abstract 6091**.

Vermorken JB et al; EORTC 24971/TAX 323 Study Group. **Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer.** *N Engl J Med* 2007b;357(17):1695-704. **Abstract**



INTERVIEW

Marshall R Posner, MD

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

Tracks 1-20

Select Excerpts from the Interview

Track 1

DR LOVE: What are the current demographic trends for head and neck cancer?

DR POSNER: The demographics are changing radically. In the past, most head and neck cancer was associated with both heavy alcohol intake and smoking.

A few cases occurred in younger people, which were cryptic in their origin and tended to be devastating.

Of course, there's an older group of people who have premalignant lesions that develop into cancer most likely related to environmental carcinogenesis or prior low-grade viral infections.

However, over the last decade and a half, there has been a marked increase in cancer at the base of the tongue and in the tonsils in young nonsmokers and nondrinkers.

The typical patient is between 45 and 55 years of age and has a two- to three-year history of smoking in college. They present with a painless mass in the neck that is found to be squamous cell or an identified primary in the tonsils or base of the tongue in association with a painless mass in the neck.

These are almost always HPV-16-positive. In fact, 60 to 70 percent of all tonsillar or base-of-tongue tumors in this country are being described as HPV-16-positive or associated with another carcinogenic HPV type found in the current vaccine.

Track 5

DR LOVE: Can you talk about some of the key recent research developments in this tumor?

DR POSNER: The biggest development has been the use of targeted agents. We now see cetuximab and EGFR antagonists coming into the clinic. The radiation therapy/cetuximab data (Bonner 2006) are intriguing. It's still difficult to substitute that regimen for traditional chemoradiation therapy simply because there's only one good study.

On the other hand, multiple studies show that cisplatin with radiation therapy is more effective than radiation therapy alone (Brizel 1998; Cooper 2004; Bernier 2004).

Over the next three or four years, cetuximab will be integrated into chemotherapy and chemoradiation therapy regimens in a more robust fashion, which I believe will be productive.

Interestingly enough, at ASCO 2007 the EORTC presented the EXTREME study of platinum/5-FU with cetuximab versus platinum/5-FU alone as first-line therapy for recurrent disease. The study demonstrated a significant improvement in overall survival, with the median duration increasing from 7.4 to 10.1 months (Vermorken 2007a; [1.3]).

This is the first time in head and neck cancer research that a combination of drugs was shown to be superior to any other combination for recurrent disease. It's hard to demonstrate improvements in recurrent disease. It's only when we evaluate these three-drug regimens — and particularly with a targeted noncross-resistant drug like cetuximab — that we see an additive effect.

Track 10

DR LOVE: Can you review some of the key clinical trials evaluating chemotherapy in the neoadjuvant setting?

DR POSNER: The neoadjuvant setting is undergoing an evolution. For the first time, we have established that a three-drug regimen, docetaxel/platinum/5-FU, is superior to platinum/5-FU. As a result, survival has been improved compared to platinum/5-FU, which had shown improved survival compared to radiation therapy or surgery. Three trials have evaluated docetaxel/platinum/5-FU (Calais 2006; Vermorken 2007b; Posner 2007).

One trial by Calais, reported at ASCO 2006, was a larynx preservation trial for larynx and pyriform sinus cancers. A significant improvement was demonstrated in the laryngeal preservation rate for patients treated with three cycles of docetaxel/cisplatin/5-FU (TPF) compared to those treated with three cycles of cisplatin/5-FU (PF) as induction therapy (Calais 2006; [2.1]). Although it's not clear at this time, there may be a survival advantage as well. However, that will depend on further analysis of the data as they mature.

TAX-323/EORTC-24971 compared four cycles of TPF to four cycles of PF followed by radiation therapy for all patients with unresectable disease. Patients who received TPF had about a 30 percent reduction in mortality and an improvement in progression-free and overall survival (Vermorken 2007b; [2.2]).

2.1

GORTEC 2000-01: Efficacy and Tolerability of Induction Docetaxel/Cisplatin/5-FU (TPF) in Patients with Hypopharyngeal and Laryngeal Cancer

	TPF n = 106	PF n = 99	*p*-value
Overall response rate*	82.8%	60.8%	0.0013
Complete response	43.4%	30.4%	
Partial response	39.4%	30.4%	
Three-year larynx preservation rate	63.2%	41.1%	0.036
Adverse events (>Grade III)			
Alopecia	19.0%	2.1%	0.002
Mucositis	5.1%	9.2%	0.04
Neutropenia	56.5%	35.4%	0.03
Febrile neutropenia	2.1%	6.9%	0.045
Thrombocytopenia	2.1%	6.5%	0.2
Anemia	6.2%	7.3%	0.3

* Tumor and nodes

SOURCE: Calais G et al. Presentation. ASCO 2006;**Abstract 5506**.

2.2

TAX-323/EORTC-24971: Docetaxel/Cisplatin/5-FU (TPF) versus Cisplatin/5-FU (PF) Followed by Radiation Therapy for Patients with Unresectable Head and Neck Cancer

Parameter	TPF (n = 177)	PF (n = 181)	HR (95% CI)	*p*-value
Progression-free survival (months)	11.0	8.2	0.72 (0.57-0.91)	0.007
One-year	48%	31%		
Two-year	25%	20%		
Three-year	17%	14%		
Overall survival (months)	18.8	14.5	0.73 (0.56-0.94)	0.02
One-year	72%	55%		
Two-year	43%	32%		
Three-year	37%	26%		
Response after induction chemotherapy				
Overall	68%	54%		0.006
Complete response	8.5%	6.6%		
Partial response	59.3%	47.0%		
Response after chemotherapy followed by radiation therapy				
Overall	72%	59%		0.006
Complete response	33.3%	19.9%		
Partial response	39.0%	38.7%		
Duration of response (months)	15.4	11.6	0.74 (0.53-1.03)	0.08

"Our study showed that induction chemotherapy with TPF resulted in significant and clinical meaningful improvements in outcomes, as compared with PF, in locoregionally advanced, unresectable squamous-cell carcinoma of the head and neck. Patients who were treated with TPF had a reduction of 28% in the risk of disease progression or death, as compared with those who received PF. They also had an extension of 2.8 months in median progression-free survival. This result was associated with significant improvements in overall survival, overall response rates, and time to treatment failure. Patients in the TPF group had a reduction of 27% in the risk of death, an improvement in median overall survival of 4.3 months, and an absolute increase in 3-year survival of 10.9%."

SOURCE: Vermorken JB et al. *N Engl J Med* 2007b;357(17):1695-704. **Abstract**

The third trial, TAX-324, was an international trial that included patients with resectable or unresectable disease. We administered three cycles of a more aggressive TPF regimen (docetaxel 75 mg/m^2, cisplatin 100 mg/m^2 and 5-FU 1,000 mg/m^2/day, days 1-4, q3wk) and compared it to PF (cisplatin 100 mg/m^2 and 5-FU 1,000 mg/m^2/day, days 1-5, q3wk) (Posner 2007).

The induction chemotherapy was followed by concurrent chemoradiation therapy (five days per week) with bolus carboplatin (AUC 1.5 mg/mL) once a week (Posner 2007). We chose to do that to reduce the toxicity associated with the cisplatin that had been used in the past to improve the outcomes in terms of neurotoxicity and dehydration.

We saw a 30 percent reduction in mortality associated with TPF. Our three-year survival rate was 62 percent in the TPF arm versus 48 percent in the PF arm (Posner 2007; [2.3, 2.4]).

2.3

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%		

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

2.4

TAX-324: Efficacy and Safety of Induction TPF Followed by Chemoradiation Therapy

"The results of this randomized trial of therapy for locally advanced squamous-cell carcinoma of the head and neck show the advantages of induction TPF chemotherapy followed by chemoradiotherapy over induction PF followed by chemoradiotherapy. Longer overall and progression-free survival and a nonsignificant reduction in overall toxic effects were evident in the TPF group...

Patients in the TPF group had a significant reduction in reported locoregional failure, but as compared with PF, the effect of TPF on distant metastases did not differ significantly."

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

Track 16

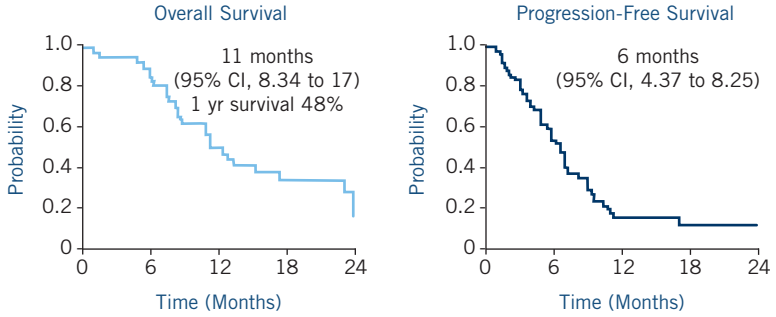
DR LOVE: What are the ongoing research strategies with the TKIs?

DR POSNER: The MD Anderson data with cisplatin/docetaxel/erlotinib are intriguing and potentially positive. Investigators conducted a Phase II trial,

which is relatively mature, in which they administered cisplatin and docetaxel at relatively high doses — 75 mg/m^2 every three weeks for each — and erlotinib at 150 mg daily. Patients received six cycles of treatment if they continued to respond and then went on to maintenance erlotinib until they had progressive disease or toxicity (Kim 2007). They had almost a 50 percent one-year survival rate, which is good for recurrent disease. Four patients (eight percent) had a complete response, 28 patients (58 percent) had a partial response and 13 (25 percent) had stable disease (Kim 2007; [2.5]). ■

2.5

Efficacy of Erlotinib/Docetaxel/Cisplatin in an Open-Label, Phase II, Single-Center Study for Patients with Advanced or Recurrent Head and Neck Cancer



SOURCE: With permission from Kim ES et al. Presentation. ASCO 2007;**Abstract 6013**.

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Bernier J et al. **Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer.** *N Engl J Med* 2004;350(19):1945-52. **Abstract**

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**

Brizel DM et al. **Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer.** *N Engl J Med* 1998;338(25):1798-804. **Abstract**

Calais G et al. **Randomized phase III trial comparing induction chemotherapy using cisplatin (P) fluorouracil (F) with or without docetaxel (T) for organ preservation in hypopharynx and larynx cancer. Preliminary results of GORTEC 2000-01.** *Proc ASCO* 2006;**Abstract 5506**.

Cooper JS et al. **Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck.** *N Engl J Med* 2004;350(19):1937-44. **Abstract**

Kim ES et al. **Final results of a phase II study of erlotinib, docetaxel and cisplatin in patients with recurrent/metastatic head and neck cancer.** *Proc ASCO* 2007;**Abstract 6013**.

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

Vermorken J et al. **Cetuximab extends survival of patients with recurrent or metastatic SCCHN when added to first line platinum based therapy — Results of a randomized phase III (Extreme) study.** *Proc ASCO* 2007a;**Abstract 6091**.

Vermorken JB et al. **Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer.** *N Engl J Med* 2007b;357(17):1695-704. **Abstract**

INTERVIEW

Walter J Curran Jr, MD

Dr Curran is Professor and Chairman in the Department of Radiation Oncology and is Deputy Director for Clinical Sciences at Thomas Jefferson University's Kimmel Cancer Center of Jefferson Medical College in Philadelphia, Pennsylvania.

Tracks 1-13

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss the use of induction chemotherapy followed by chemoradiation therapy versus chemoradiation therapy alone in the clinical setting?

DR CURRAN: Until the last two or three years, induction chemotherapy had fallen out of favor as not showing a substantial benefit. However, several trials, most notably the Phase III TAX-324 trial (Posner 2007), have demonstrated that a docetaxel-based induction regimen administered prior to radiation therapy with a relatively nonintense concurrent chemotherapy regimen was superior (2.3, 2.4).

These findings made people realize that a role may exist for induction therapy. It should not, however, be administered instead of concurrent therapy, except to those patients for whom concurrent therapy is not feasible.

TAX-324 demonstrated that a benefit exists with docetaxel-based induction therapy (Posner 2007). The trial, however, doesn't tell us whether it is superior to the more intense day-one chemoradiation therapy regimen used in the RTOG trial, which evaluates a docetaxel-based induction regimen prior to chemoradiation therapy versus a full-dose platinum and radiation therapy regimen on day one.

DR LOVE: Has docetaxel been used as part of concurrent chemoradiation therapy?

DR CURRAN: Yes, and there have been some promising results. It can be administered on a weekly or an every three-week schedule. Either way, the complete response rates and the progression-free survival rates appear to be reasonable.

DR LOVE: Can you discuss the side effects and toxicity associated with induction therapy and chemoradiation therapy?

DR CURRAN: With induction therapy, the toxicities are the same as one might see with any full-dose, every three-week taxane- or platinum-based regimen — hematologic depression, stomatitis, risk of infection. Chemoradiation therapy to the head and neck may be one of the most challenging cancer therapies any patient goes through. In addition to the effects of the chemotherapy, you also have the enhancement of the radiation effects by the chemotherapy.

Grade III mucositis is a highly predictable side effect. Most patients who are going to receive radiation therapy to substantial portions of their mucosa need to have a PEG tube inserted prior to its initiation. It's not a situation in which a feeding tube should be placed only after a certain amount of weight loss. It must be considered as part of the approach.

One concern early in the chemoradiation-therapy era was whether such intense regimens would result in radiation treatment delays, which we know are deleterious to tumor control. With the feeding tube and outstanding supportive care, most patients can get through radiation therapy without substantial treatment interruptions.

We find that providing the patient with a three-day weekend once or twice during a seven-week course, which doesn't extend the treatment time, can be a godsend. This is not considered even a minor protocol violation if a patient happens to be involved in a clinical trial.

Track 5

DR LOVE: Can you talk about the use of cetuximab in head and neck cancer?

DR CURRAN: Cetuximab is a monoclonal antibody that targets the epidermal growth factor receptor (EGFR). Head and neck tumors that overexpress

EGFR are associated with a worse prognosis in terms of recurrence and survival. EGFR is a highly relevant target for head and neck cancer.

Initially, cetuximab was studied in patients with head and neck cancer in a Phase I pilot study, which demonstrated that it was well tolerated, could be administered weekly during a course of radiation therapy and produced promising results (Robert 2001).

That trial led to an international Phase III study in which patients with Stage III or IV SCCHN were randomly assigned to treatment with radiation therapy alone or radiation therapy and weekly cetuximab (Bonner 2006).

A statistically significant improvement in survival and disease control was found for the patients in the cetuximab-containing arm (Bonner 2006; [3.1]). Interestingly, the magnitude of benefit was almost identical to what was seen when we evaluated radiation therapy with cisplatin versus radiation therapy alone.

The difference was we did not observe the enhancement of mucositis, stomatitis and locoregional toxicity that is associated with cisplatin, nor the hematologic toxicity (Bonner 2006; [3.1]). This trial allows us to consider another tool in our armamentarium for patients with head and neck cancer.

DR LOVE: Can you talk more about the eligibility and design of that trial?

DR CURRAN: It was a one-to-one randomized Phase III design. Patients could have Stage III or IV SCCHN. Some patients had high-risk tumors that were resected. Others had unresected disease, but in general they did not have bulky, bilateral, fixed lymph nodes.

The overlap in eligibility between this study and the typical Phase III RTOG trial for Stage III/IV head and neck cancer was substantial, but this study included patients with slightly more intermediate- rather than high-risk locoregional head and neck cancer (Bonner 2006).

3.1

Radiation Therapy with Cetuximab for SCCHN

"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**

The median duration of overall survival was substantially higher — about a 50 percent increase. The absolute survival benefit at three years was 10 percent, but it was statistically significant, with a good hazard ratio and a *p*-value of 0.05 (Bonner 2006; [3.1]).

Track 7

DR CURRAN: The question I hear frequently is, "Do I use chemoradiation therapy or do I use chemotherapy with cetuximab? Or do I add cetuximab to chemoradiation therapy?" Without having a final answer, the data we need are on the safety of chemoradiation therapy with cetuximab.

The most mature data come from a Phase II study at Memorial Sloan-Kettering in which patients received an altered fractionation regimen of radiation therapy, relatively aggressive concurrent chemotherapy and cetuximab (Pfister 2006).

A few years ago this study closed early due to concern over some early deaths (Pfister 2003). When a mature manuscript was published in the *Journal of Clinical Oncology* last year, we saw that those early deaths were probably not treatment or cetuximab related. The absolute survival, even accounting for those early deaths, and tumor control were outstanding (Pfister 2006; [3.2]).

RTOG has completed accrual to a randomized Phase II study in which one arm receives radiation therapy, docetaxel and cetuximab (3.3), and the other arm receives radiation therapy, cisplatin and cetuximab. We have not observed any toxicity that made us feel we had to close the study early, but we don't have the final results.

We have accrued about a third of the target number of patients in RTOG-0522, which is evaluating radiation therapy/cisplatin versus radiation therapy/cisplatin/cetuximab (1.2, page 5). I am questioned about why we don't have a third arm of radiation therapy/cetuximab.

We initially proposed that, but because that would have been equivalent to platinum and we would have been looking for a reduction in toxicity, it would have tripled the required number for accrual, which would have exceeded the feasible range of patient numbers.

3.2 **Phase II Trial of Concurrent Cetuximab, Cisplatin and Concomitant Boost Radiation Therapy for Patients with Locoregionally Advanced SCCHN**

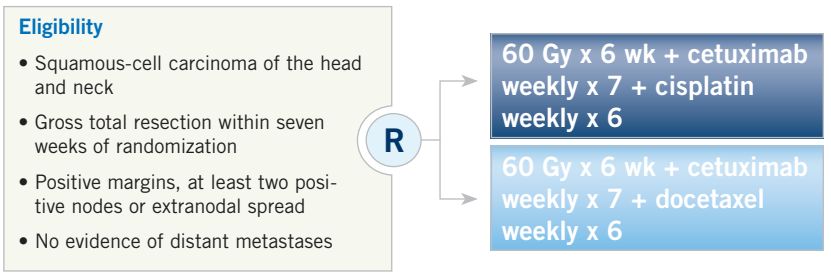
"With a median follow-up time of 52 months, the 3-year overall survival rate was 76%, which is superior to the historical experience at our institution for a predominantly stage IV population receiving cisplatin concurrent with delayed, accelerated radiotherapy for SCCHN. Progression-free survival and locoregional control rate were similarly encouraging. These survival data also compare favorably with those reported in the major published randomized trials supporting concurrent chemoradiotherapy."

SOURCE: Pfister DG et al. *J Clin Oncol* 2006;24(7):1072-8. **Abstract**

3.3

Phase II Study of Adjuvant Cetuximab and Chemoradiation Therapy with Cisplatin or Docetaxel for Patients with Resected Stage III or IV SCCHN

Protocol IDs: RTOG-0234, NCT00084318
Accrual: 230 (Closed)



SOURCE: NCI Physician Data Query, October 2007.

For a patient who has a marginal indication for the addition of systemic therapy to radiation therapy but for whom you want to do more than radiation therapy, I recommend cetuximab. Among older patients, cetuximab is clearly well tolerated. For the patients with advanced disease, which would not have been included in the Bonner study, I would use chemotherapy if they could tolerate it. The patients in that middle zone are the challenging group. If a physician has a good discussion with the patient, and they want to use a regimen with Phase II but not Phase III data, I believe chemoradiation therapy and cetuximab is reasonable.

Track 9

DR LOVE: What about patients who have head and neck cancer but also have comorbidities such as alcohol abuse, malnutrition or heavy smoking histories?

DR CURRAN: Those are challenging medical and social issues. Clearly continued use of tobacco has been associated with a poor outcome for patients with this type of tumor. Anything that physicians can do to help patients with pharmacologic and social tools to quit smoking before therapy begins will help the patient. The same is true for alcohol abuse.

Older gentlemen with all those problems are simply one facet of head and neck cancer. We're seeing more people who don't have a substantial history of tobacco or alcohol use. We're seeing younger women and more demographic diversity. I can't tell you why, but this is something we're seeing in trial enrollment and elsewhere. We hope to see stronger advocacy on behalf of such patients. It's a disease that needs advocacy as much as any disease because both the tumor and its treatment can be disabling and disfiguring. Any support we can give to patients who suffer from this will be tremendous.

My father passed away a couple years ago from head and neck cancer. Having him tell me he didn't want to eat in public because of the disfigurement and the other problems brought home the issues we're dealing with.

DR LOVE: Did that change your perspective as a clinician or researcher?

DR CURRAN: It was probably more of a personal nature than professional, but certainly, seeing it from the point of view of the family does bring home the issues. Seeing someone disabled, or his perception of disability, was probably the strongest personal lesson — seeing him affected to the point of refusing to go out in public because of his perception of his image. I believe other people felt his appearance was less of a problem than he did himself — that was probably the most poignant difficulty. ■

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**

Calais G et al. **Randomized phase III trial comparing induction chemotherapy using cisplatin (P) fluorouracil (F) with or without docetaxel (T) for organ preservation in hypopharynx and larynx cancer. Preliminary results of GORTEC 2000-01.** *Proc ASCO* 2006;**Abstract 5506**.

Cooper JS et al. **Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck.** *N Engl J Med* 2004;350(19):1937-44. **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**

Gebbia V et al. **Cetuximab in squamous cell head and neck carcinomas.** *Ann Oncol* 2007;18(Suppl 6):vi5-7. **Abstract**

Kim ES et al. **Final results of a phase II study of erlotinib, docetaxel and cisplatin in patients with recurrent/metastatic head and neck cancer.** *Proc ASCO* 2007;**Abstract 6013**.

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Pfister DG et al. **Concurrent cetuximab, cisplatin, and concomitant boost radiation therapy (RT) for locoregionally advanced, squamous cell head and neck cancer (SCCHN): Preliminary evaluation of a new combined-modality paradigm.** *Proc ASCO* 2003;**Abstract 1999**.

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**

Remenar E et al. **A randomized phase III multicenter trial of neoadjuvant docetaxel plus cisplatin and 5-fluorouracil (TPF) versus neoadjuvant PF in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN). Final analysis of EORTC 24971 [TAX 323].** *Proc ASCO* 2006;**Abstract 5516**.

Robert F et al. **Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer.** *J Clin Oncol* 2001;19(13):3234-43. **Abstract**

Salama JK et al. **Chemoradiotherapy for locally advanced head and neck cancer.** *J Clin Oncol* 2007;25(26):4118-26. **Abstract**

Vermorken JB et al; EORTC 24971/TAX 323 Study Group. **Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer.** *N Engl J Med* 2007;357(17):1695-704. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **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

2. **RTOG-0522 will determine whether the addition of _____ to cisplatin/radiation therapy will improve outcomes among patients with locally advanced tumors.**
   a. Cetuximab
   b. Docetaxel
   c. Bevacizumab
   d. Both a and b
   e. Both b and c

3. **Induction therapy with docetacel/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

4. **The EXTREME study demonstrated that a three-drug combination of _____ was better than a two-drug combination as first-line therapy for patients with recurrent, metastatic head and neck cancer.**
   a. Docetaxel/platinum/5-FU
   b. Cetuximab/platinum/5-FU
   c. Both a and b
   d. None of the above

5. **Among patients with larynx or pyriform sinus cancer, the laryngeal preservation rate was improved with the addition of _____ to cisplatin/5-FU as neoadjuvant therapy.**
   a. Erlotinib
   b. Bevacizumab
   c. Docetaxel
   d. Cetuximab
   e. None of the above

6. **Among patients with unresectable head and neck cancer, overall survival was improved with the addition of _____ to cisplatin/5-FU as induction therapy prior to radiation therapy.**
   a. Erlotinib
   b. Bevacizumab
   c. Docetaxel
   d. Cetuximab
   e. None of the above

7. **Data from TAX-324 demonstrated a _____ reduction in mortality among patients with SCCHN who were treated with TPF compared to those treated with PF as induction therapy prior to chemo-radiation therapy.**
   a. Five percent
   b. 10 percent
   c. 20 percent
   d. 30 percent

8. **An open-label Phase II trial of erlotinib, docetaxel and cisplatin demonstrated a one-year survival rate of almost _____ for patients with advanced or recurrent head and neck cancer.**
   a. 90 percent
   b. 70 percent
   c. 50 percent
   d. 30 percent

9. **The addition of cetuximab to radiation therapy enhances the common side effects associated with radiation therapy of the head and neck, such as mucositis, xerostomia, dysphagia, pain and weight loss.**
   a. True
   b. False

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

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To what extent does this issue of *HNCU* address the following global learning objectives?

- Critically evaluate the implications of emerging clinical trial data on the treatment of head and neck cancer, and incorporate these data into management strategies in the local, locally advanced, recurrent and metastatic disease settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials . . . . . 5 4 3 2 1 N/A
- Review the contributing etiologic factors relevant to the development of head and neck tumors, and explain how they impact patient-specific prognosis and treatment decisions . . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for the multidisciplinary management of head and neck cancer, integrating the roles of the practicing head and neck surgeon, radiation oncologist, medical oncologist and other healthcare professionals delivering necessary ancillary care and support . . . . . 5 4 3 2 1 N/A
- Review the existing and evolving clinical trial data demonstrating the benefit and safety of EGFR-directed single-agent and combined therapy in the front-line and progressive-disease settings, and explain how this molecular pathway impacts tumorigenesis . . . . . 5 4 3 2 1 N/A
- Discuss adverse effects associated with the treatment of head and neck cancer and their impact on selection of therapy and patient quality of life . . . . . 5 4 3 2 1 N/A
- Identify consensus-based acute and prophylactic strategies to manage dermatotoxicities associated with the clinical use of EGFR inhibitors . . . . . 5 4 3 2 1 N/A
- Describe the psychosocial implications of harboring a tumor of the head or neck and offer strategies to improve long-term physical outcomes and assist patients with disease coping . . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Edward S Kim, MD	5 4 3 2 1	5 4 3 2 1
Marshall R Posner, MD	5 4 3 2 1	5 4 3 2 1
Walter J Curran Jr, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
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HNCU107

Head & Neck Cancer™

U P D A T E

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Head & Neck Cancer™

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This program is supported by educational grants from
ImClone Systems and Sanofi-Aventis.

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Last review date: December 2007
Release date: December 2007
Expiration date: December 2008
Estimated time to complete: 3.25 hours