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

Track 8 Clinical therapeutic options for patients with locally advanced H&N cancer

Track 9 Cytoprotective effects of IMRT in H&N cancer

Track 10 Targeted agents under investigation in H&N cancer

Track 11 Targeting VEGF, EGFR and RET with the tyrosine kinase inhibitor vandetanib

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

Track 13 Delineation of a genomic profile of HPV-related oropharyngeal cancer

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**.