

# CLINICAL TRIALS Broadcast

In Focus: Head and Neck Carcinomas

## 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

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### Background

Efforts to improve treatment outcomes among patients with locally advanced (stage III-IV) squamous cell carcinoma of the head and neck (SCCHN) have been ongoing for decades. As recently as the early to mid-1990s, radical surgical resection, often with adjuvant radiotherapy, was the treatment of choice, despite its association with diminished quality of life. Clinical trials of potentially improved approaches found that hyperfractionation and some accelerated fractionation regimens demonstrated increased locoregional control (LRC) and, in some studies, survival.<sup>1</sup> For example, the Radiation Therapy Oncology Group (RTOG) study 90-03 compared standard fractionation (SFX), hyperfractionation (HFX), accelerated fractionation with split course (AFX-S), and accelerated fractionation by concomitant boost (AFX-CB) among patients with stage III-IV SCCHN. According to the reported results, AFX-CB and HFX were associated with significantly higher LRC rates compared with SFX.<sup>2</sup> HFX being quite costly and labor intensive, the study authors recommended AFX-CB as the standard radiation therapy for intermediate-stage SCCHN and further testing for more advanced disease. The RTOG 0129 study is evaluating AFX-CB plus cisplatin versus SFX plus cisplatin and has recently completed patient enrollment.

Other recent studies suggest that concurrent chemotherapy and radiation therapy would be more beneficial than radiation alone in terms of LRC and survival rates for patients with locally advanced disease.<sup>3-6</sup> In addition, postoperative adjuvant radiation and chemotherapy have also been found to be of benefit.<sup>7,8</sup> To avoid the systemic and mucosal toxicities associated with the high-dose intermittent cisplatin regimen that was used in ear-

lier trials, several studies have evaluated the efficacy of alternative cisplatin regimens. The findings suggest that a cumulative cisplatin dose of 200 mg/m<sup>2</sup> given every 3 weeks, weekly, or daily during radiation therapy, yields therapeutic benefit.<sup>6,9,10</sup>

The most extensively studied regimen and, consequently, the one considered the current standard of care for locally advanced SCCHN (for nonsurgery patients) is conventionally fractionated radiation therapy (70 Gy in 35 fractions over 7 weeks) with cisplatin 100 mg/m<sup>2</sup> every 3 weeks.

In recent years, studies have found that epidermal growth factor receptor (EGFR) may play a role in predicting and modulating the response of SCCHN patients to radiation.<sup>11-14</sup> Based on these findings, a phase III trial was designed in order to study whether combining the anti-EGFR monoclonal antibody cetuximab with radiation therapy would improve outcomes compared with radiation alone. According to the findings, the combination was associated with improvements both in local-regional disease control and in overall survival. Compared with radiotherapy alone, the cetuximab-plus-radiotherapy regimen was associated with a hazard ratio (HR) for locoregional progression of 0.68 ( $P=.005$ ), an HR for death of 0.74 ( $P=.03$ ).<sup>15</sup> The addition of cetuximab was not associated with added hematologic or mucosal toxicities compared with radiation alone.

RTOG 0522 will assess whether adding cetuximab to radiation plus cisplatin will improve survival and/or LRC among patients with stage III-IV SCCHN. Two hypotheses are addressed: (1) as EGFR affects cellular response to radiation and cytotoxic agents, the addition of a neutralizing antibody (cetuximab) to radiation plus cisplatin will enhance response and improve disease-free survival, and (2) the addition of cetuximab will improve overall survival without added toxicity and will improve LRC.

The control arm, radiation therapy plus cisplatin, was selected based on the results of RTOG 99-14.<sup>16</sup> Although the study is still ongoing, the 2-year overall survival and disease-free survival rates of 71.6% and 53.5%, respectively, are encouraging and provide enough evidence to employ this regimen in the present phase III study. The experimental arm has not yet been tested in a multi-institutional study. However, a single-institution study with 22 patients demonstrated an estimated 3-year survival rate of 76% and toxicities similar to those seen with radiation plus cisplatin alone.<sup>17</sup>

Finally, a large randomized Danish study found that AFX delivered in 6 fractions per week yielded a better LRC rate than SFX given in 5 fractions per week.<sup>18</sup> In the present study, AFX by intensity-modulated radiation therapy (IMRT) will be delivered in 6 fractions per week during 5 of the 6 treatment weeks.

## References

1. Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: Altered fractionation regimens. *The Lancet Oncol.* 2002;3:693-701.
2. Fu KK, Pajak TF, Trotti A, et al. A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Onc Biol Phys.* 2000;48:7-16.
3. Adelstein DJ, Li Y, Adams GL, 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;21:92-98.
4. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *NEJM.* 2003;349:2091-2098.
5. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: A randomized multicenter study. *J Clin Oncol.* 1998;16:1318-1324.
6. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *J Clin Oncol.* 2000;18:1458-1464.
7. Bernier J, Dommene C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350:1945-1952.
8. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350:1937-1944.
9. Huguenin P, Beer KT, Allal A, et al. Concomitant cisplatin significantly improves loco-regional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *J Clin Oncol.* 2004;22:4665-4673.
10. Wee J, Tan EH, Tai BC, et al. Phase III randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with AJCC/UICC (1997) stage 3 and 4 nasopharyngeal cancer of the endemic variety. *Proc Am Soc Clin Oncol.* 2004;23:487.
11. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern. *Cancer Res.* 2002;62:7350-7356.
12. Ang KK, Andrantschke NH, Milas L. Epidermal growth factor receptor and response of head-and-neck carcinoma to therapy. *Int J Radiat Onc Biol Phys.* 2004;58:959-965.
13. Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. *J Clin Oncol.* 2003;21:2787-2799.
14. Harari PM, Huang S-M. Combining EGFR inhibitors with radiation or chemotherapy: will preclinical studies predict clinical results? *Int J Radiat Onc Biol Phys.* 2004;58:976-983.
15. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354:567-578.
16. Ang KK, Harris J, Garden AS, et al. Concomitant boost radiation plus concomitant cisplatin for advanced head and neck carcinomas: a phase II trials of the Radiation Therapy Oncology Group (RTOG 99-14). *J Clin Oncol.* 2005;23:3008-3015.
17. Pfister DG, Su YB, Kraus DH, 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;24:1072-1078.
18. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomized controlled trial. *Lancet.* 2003;362:933-940. Erratum in: *Lancet.* 2003;362:1588.

## Objectives

### Primary Objective

- Evaluate whether the addition of cetuximab to a concurrent radiation-cisplatin regimen will improve disease-free survival in patients with locally advanced SCCHN

### Secondary Objectives

- Assess the impact of the addition of cetuximab to a concurrent radiation-cisplatin regimen on the following: overall survival of patients with locally advanced SCCHN, LRC of patients with locally advanced SCCHN, acute and late toxicities, quality of life and health utilities
- Correlate the expression of EGFR and its downstream molecules and pretreatment positron emission tomography (PET) scan findings with outcome in patients participating in this component of the trial
- Correlate pretreatment PET scan findings with disease-free survival, overall survival, and LRC in patients participating in this component of the trial
- Correlate posttreatment PET scan findings with nodal response and nodal relapse in patients participating in this component of the trial.

## Basic Eligibility Criteria

- Histologically proven stage III or IV SCCHN
- No distant metastases
- Zubrod performance status 0-1
- At least 18 years of age
- Adequate bone marrow, hepatic, and renal function
- No prior invasive malignancy (except nonmelanomatous skin cancer) unless disease free for  $\geq 3$  years
- No prior systemic therapy for SCCHN
- No prior radiation therapy that would overlap with radiation therapy fields in study
- No prior primary tumors in oral cavity, nasopharynx, sinuses, or salivary glands.

## Targeted Accrual

Approximately 720

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## Schema

