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Current Status of Anti Epidermal Growth Factor Receptor Therapy in the Curative Treatment of Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Squamous cell carcinoma of head and neck is the most common malignancy of the upper aero digestive tract in the world. In this article, we attempt to summarize the role of anti-epidermal growth factor therapy (EGFR) in the treatment of locally advanced head and neck squamous cell carcinoma. Cetuximab plus radiotherapy is a reasonable alternative in patients who cannot tolerate standard concurrent chemoradiotherapy (CTRT). There is no benefit by adding targeted therapy in addition to standard CTRT. Trials evaluating the role of targeted agents in the adjuvant setting showed no benefit in patients with high risk features; in addition to standard post-operative CTRT. Role of adjuvant monoclonal antibody in patients with intermediate risk factors is being evaluated.

KEYWORDS: Epidermal growth factor receptor (EGFR); Head and neck-targeted therapy.

INTRODUCTION

Head and neck cancer accounts for more than 600,000 cases annually worldwide.[1] It is estimated that 57.7% of global head and neck cancers occurs in Asia.[2] Single modality treatment either surgery or radiotherapy remains the standard of care for early disease (Stage I & II). Majority of the patients with Head and Neck Squamous Cell Carcinoma (HNSCC) present at an advanced stage and requires surgery followed by adjuvant treatment or concurrent chemoradiation (CTRT).[3,4] Over a period of last two to three decades there is a paradigm shift from surgery to organ preservation strategies to improve the quality of life without compromising the overall survival.[4] Treatment regimens combining radiotherapy and chemotherapy are associated with significant acute and chronic toxicities.[5] The incorporation of induction chemotherapy prior to concurrent chemoradiation has not shown any additional benefit to CTRT alone.[6-9] These facts have led researchers to focus on a more cellular level to identify and study cellular targets which may have a role in cancer genesis and cell proliferation. Out of the various molecular markers that have been studied, Epidermal Growth Factor Receptor (EGFR) remains the most robustly studied and proven marker in head and neck cancers.

Epidermal growth factor receptor (EGFR) protein expression is detected in 90% of all HNSCC tumours.[9] EGFR is a 170-180 kd trans membrane glycoprotein tyrosine kinase receptor. It binds Epidermal growth factor (EGF), Transforming growth factor-alpha (TGF-α), and other regulating proteins. Activation of EGFR results in a complex cascade of signaling pathways that influence normal cellular proliferation and differentiation which lead to strong mitogenic activity. Ligand binding results in receptor dimerization, activation of the intrinsic kinase domain, and phosphorylation of tyrosine residues within the cytoplasmic tail. Proteins dock on the phosphorylated residues, leads to the activation of signaling pathways that promote cell growth, proliferation, differentiation, and migration.

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High levels of EGFR protein expression is associated with decreased survival, resistance to radiotherapy, loco regional treatment failure, and increased rates of distant metastases.[10] The concept of blockade of epidermal growth factor receptor signaling pathway for anti-proliferative antitumor activity was introduced in the 1980s.[11,12] EGFR inhibitors block the EGFR phosphorylation and subsequent tumor cell proliferation.[13,14] EGFR inhibitors include monoclonal antibodies (mAb) that block the extracellular ligand-binding domain, and small molecule inhibitors (Tyrosine kinase inhibitors -TKI) that inhibit activation of the intracellular cytoplasmic tyrosine kinase.

This review article will try to enumerate the currently available clinical trial data regarding EGFR inhibitors in Head and Neck Squamous Cell Carcinoma (HNSCC), treated with curative intend. There are many monoclonal antibodies and TKIs, that have been evaluated in the treatment of HNSCC, their mechanism of action, and mode of administration is illustrated in Table 1.

ROLE OF EGFR INHIBITORS IN THE DEFINITIVE RT/CTRT SETTING

Concurrent chemoradiotherapy is the standard of care in patients with locally advanced HNSCC who are considered for non-surgical approach and is associated with increased toxicity.[5] Various phase II trials have addressed the role of EGFR inhibitors in the definitive setting along radiotherapy or concurrent chemoradiation and are summarized in Table 2.

All the phase II trials did not show any added benefit in addition to RT or CTRT except Nimozutumab. The positive

Agent	Mechanism/target/binding	Method of administration
Cetuximab	Chimeric anti-EGFR mAb	IV
Nimotuzumab	Humanized anti-EGFR mAb	IV
Panitumumab	Fully human anti-EGFR mAb	IV
Zalutumumab	Fully human anti-EGFR mAb	IV
Gefitinib	Reversible, small-molecule EGFR TKI	PO
Erlotinib	Reversible, small-molecule EGFR TKI	PO
Lapatinib	Reversible, small-molecule EGFR/ErbB2 TKI	PO
Afatinib (BIBW 2992)	Irreversible, small-molecule ErbB family inhibitor	PO
PF-00299804	Irreversible, small-molecule pan-HER TKI	PO

IV: Intra Venous; PO: Per Oral; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitor

Table 1: EGFR inhibitors evaluated in head and neck cancer.

Study	Patients	Methods	Outcome	Remarks
Gefitinib[15] 2012	n=31	CTRT+Gefitinib	3-year DFS 42.9% 3-year OS 48.4%	EGFR expression did not predict for response or survival
Lapatinib[16] 2013	n=33 n=34	CTRT *vs.* CTRT+lapatinib	The median PFS 35.3 *vs.*12.1 months (p=0.18) median OS-30.9 months (p=0.382)	No difference in PFS or OS
Erlotinib[17] 2013	n=99 n=105	Elrotinib+CTRT *vs.* CTRT alone	CRR 52% *vs.* 40% No improvement in PFS (p=0.71) or OS (p=0.88)	No benefit
Nimotuzumab[18] 2014	n=23 n=23 n=23 n=23	Nimotuzumab+ CTRT *vs.* CTRT alone Nimotuzumab + RT *vs.* RT alone	Median 5-year PFS was 54.24 months (CRT+nimotuzumab) 14.95 months (CRT) (p= 0.036). 14.29 months (RT+nimotuzumab) 9.76 months (RT arms) (p= 0.41)	Targeted agents provides survival benefit to patients with inoperable advanced disease
Panitumumab[19] 2015	n=64 n=89	CTRT *vs.* CTRT+ panitumumab	PFS at 2 years 65% *vs.* 61% (p= 0·03) OS at 2 years 78% *vs.* 69% (p= 0·1.0)	No additional benefit with Panitumumab

Table 2: Anti EGFR agents tested in phase II trials along with RT/CTRT.

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result obtained in the Nimotuzumab study needs to be validated in a phase III trial.

PHASE III TRIALS ADDRESSING THE ROLE OF EGFR INHIBITORS

Cetuximab is the first monoclonal antibody evaluated in a phase III trial in HNSCC. Concurrent cetuximab plus RT was evaluated in a multinational randomized study by Bonner et al in 424 patients with loco regionally advanced HNSCC.[20] They were randomly assigned to receive radical radiotherapy, either conventional dose or altered fractionation alone (n=213) or radiotherapy plus cetuximab (n=211). Cetuximab was given a loading dose of 400 mg/m^2 one week prior to RT, followed by 250 mg/m^2 weekly along with RT. With a median followup of 54 months, addition of cetuximab improved both loco regional control (50% *vs.* 41%, p= 0.006) and overall survival (three-year survival 55% *vs.* 45%, p= 0.03) compared with RT alone. A subset analysis conducted showed that the benefit of cetuximab plus RT was restricted to patients with a Karnofsky performance score (KPS) 90 to 100, under the age of 65 years, patients who received altered fractionation radiotherapy, and those with oropharyngeal cancer. The five year update of the trial showed sustained result and is summarized in Table 3.[21]

	RT (n=213)	RT+Cetuximab (n=211)
Median survival	29.3 months	49 months
5 yrs overall survival	36.4%	45.6%
HR-0.73, 95% CI 0.56-0.95 p=0.018		

Table 3: Five year survival data from a phase 3 randomized trial.[21]

Patients developed a characteristic cetuximab-induced acne form rash during treatment and generally resolved completely in the first weeks following the cessation of therapy. Patients with prominent rash had more than two and a half times longer overall survival than did patients with mild rash. It was explained as acne form rash is a biomarker of an immunological response and studies are conducted to identify patients who might benefit from maintenance cetuximab therapy.[21]

The major drawback of the trial was that it compared cetuximab plus RT with RT alone, which is no longer considered a standard approach for patients with loco regionally advanced disease. Another issues pointed were that different RT regimens were allowed in the trial, analysis of data were not site specific , there was lack of information regarding Quality of Life (QoL), and late complications. There is no trial directly comparing Cetuximab plus RT with concurrent chemoradiation.

The benefit of Cetuximab along with CTRT was evaluated in the randomized RTOG 0522 phase III trial.[22] In this trial, 940 patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were randomly assigned to concurrent cisplatin (100 mg/m^2 on days 1 and 22) plus accelerated RT (70 Gy in 42 fractions over six weeks) with or without concurrent cetuximab. At a median followup of 3.8 years, there was no significant difference in three-year progression-free survival, 59 *versus* 61 % (p=0.76), which was the primary endpoint of the trial.

Panitumumab, a fully humanized monoclonal antibody was evaluated in the National Cancer Institute Canada Clinical Trials Group HN.6 based on the result of subset analysis of Bonner Trial which showed benefit with altered fractionation radiotherapy with EGFR inhibitors.[23] Patients with locally advanced HNSCC were randomized to receive standard fractionation radiotherapy (70 Gy/35 over seven weeks) concurrently with cisplatin at 100 mg/m^2 intravenous (IV) for three doses on weeks one, four and seven *versus* altered fractionation radiotherapy (70 Gy/35 over six weeks) along with Panitumumab at 9 mg/kg IV for 3 doses one week prior to radiotherapy, on days 15 and 36. A total of 320 patients were recruited from December 2008 to November 2011 .With a median followup of 46.4 months, PFS of patients in the panitumab arm was not superior to chemotherapy arm (p=0.83).

In conclusion concurrent chemoradiotherapy with cisplatin remains the standard of care, for patients with locally advanced HNSCC, who can tolerate it. Patients who cannot tolerate platinum-based chemotherapy for any of a variety of reasons may benefit from the addition of cetuximab to radiotherapy. There is no added benefit for target agents in addition to standard CTRT.

In the ongoing RTOG 1016 study, patients with locally advanced p16+ oropharyngeal cancer are treated with intensity modulated radiotherapy and randomly assigned to either concurrent cetuximab (weekly)or cisplatin (on days one and 22). Results may give new insights to the inclusion of Cetuximab in the management of locally advanced p16+ oropharyngeal cancer.[24]

EGFR INHIBITORS IN ADJUVANT SETTING

Surgery followed by post-operative radiotherapy (PORT)/post-op CTRT is the standard of care in stage III/IVA patients.[25,26] Patients with intermediate risk factors like pT3-T4, pN2-N3, and nodal disease in levels IV-V, PNI+ or LVI+ merit adjuvant radiotherapy. Based on two major phase III trials, Radiation Therapy Oncology Group (RTOG) 9501 and EORTC 22931 showed additional benefit with concurrent cisplatin chemotherapy in patients with high risk features like extra capsular spread or margin positive disease. Ten-year update of the RTOG 9501 trial showed improved disease-free survival (12.3% *vs.*18.4% p=0.05), and trend towards improvement in overall survival was 19.6% *vs.* 27.1% (p=0.07), respectively in patients with high risk features.[27] EORTC 22931 showed improvement in progression free survival (47% *vs.* 36%, p=0.04) and overall survival (53% *vs.* 40%, p=0.02) and reduction in loco regional recurrences (18% *vs.* 31%, p=0.007) with concurrent cisplatin.[28] But concurrent chemotherapy was associated with more acute

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and overall toxicity. Adjuvant chemoradiation was not tolerated by patients with advanced age, renal insufficiency, auditory dysfunction, and poor performance status. Acute toxicity [GR³3] in the RTOG study was 77% *vs.* 34% (p<0.001) and 41% *vs.* 21% in the EORTC trial (p=0.001).

A combined analysis of these trials identified patients most likely to benefit were those with positive resection margins and/or extra capsular tumor extension in cervical lymph nodes.[29]

In patients with intermediate risk group, post-operative RT alone is the usual practice, but has shown suboptimal outcome in some patients. The ongoing RTOG 0920 trial is evaluating the role of Cetuximab in addition to RT. In this trial patient with intermediate-risk HNSCC following surgery are randomized to receive standard PORT with or without cetuximab.[30]

The next question was to evaluate the role of targeted agents in high risk patients, along with post-operative CTRT. RTOG 0234 is a phase II randomized trial, in which 238 high-risk patients with SCCHN were randomly assigned to 60 Gy radiation with cetuximab once per week plus either cisplatin 30 mg/m^2 or docetaxel 15 mg/m^2 once per week. With a median followup of 4.4 years, two year overall survival estimate was 69% (p=0.04) for the cisplatin arm, and 79% (p=0.001) for the docetaxel arm, and the 2-year disease-free survival (DFS) was 57% (p=0.05) and 66% (p=0.01), respectively.[31]

Lapatinib was tried in a phase III trial, in patients with resected stage III and IVA SCCHN. Patients with a surgical margin ≤5 mm and/or extra capsular extension were randomized to post-operative CTRT with either Placebo (P) or Lapatinib (L). RT was 66 Gy (2 Gy per day, five days per week) along with cisplatin 100 mg/m^2 of was administered on days 1, 22 and 43 of RT. P or L was given 1500 mg/day for up to one week prior to CTRT, during CTRT and for up to 12 months as monotherapy maintenance.[32] Median disease free survival (DFS) for Lapatinib was 53.6 months *versus* 54.6 months for placebo arm (2 sided p=0.45).When added to standard therapy Lapatinib, does not extend DFS, which was the endpoint of the trial.

The ongoing phase III trial-IHN01 study is evaluating the role of Nimotuzumab in the post-operative setting with CTRT in patients with high risk features.[33]

To conclude, the benefit of targeted therapy in patients with intermediate risk is being evaluated in an on-going clinical trial. Currently there is no proven benefit for targeted agents in high risk patients in addition to post-operative CTRT.

SUMMARY

Concurrent chemoradiation remains the current standard of care for treatment of locally advanced HNSCC in patients who are planned for organ preservation approach. Cetuximab along with radiotherapy may be considered as an alternative in patients who cannot tolerate cisplatin due to poor performance status and impaired renal function. Cetuximab in addition to standard chemoradiotherapy was not found to be beneficial, and is associated with increased toxicity. There is no benefit of adding targeted agents in the post-operative setting in patients who have high risk features in addition to standard adjuvant chemoradiation. RTOG 0920 is evaluating the role of cetuximab in patients with intermediate risk.

CONFLICTS OF INTEREST: None.

REFERENCES

1. WHO. Globocan 2012. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. International Agency for Research on Cancer. Web site. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed January 29, 2016.

2. Kulkarni MR. Head and neck cancer burden in India. *Int J Head Neck Surg.* 2013; 4(1): 29-35. doi: 10.5005/10001-1132

3. NCCN. NCCN Clinical Practice Guidelines in Oncology. Version 2. 2015. Web site. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed January 29, 2016.

4. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. 2013; 31(7): 845-852. doi: 10.1200/JCO.2012.43.6097

5. Pignon JP, le Maitre A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trials and 17,346 patients. *Radiother Oncol*. 2009; 92(1): 4-14. doi: 10.1016/j.radonc.2009.04.014

6. Cohen EEW, Theodore G, et al. Phase III Randomized Trial of Induction Chemotherapy in Patients With N2 or N3 Locally Advanced Head and Neck Cancer. *J Clin Oncol*. 2014; 32(25): 2735-2743. doi: 10.1200/JCO.2013.54.6309

7. Hitt R, Grau JJ, A. López-Pousa, et al. A randomized phase III trial comparing induction chemotherapy followed by chemo radiotherapy versus chemo radiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol*. 2014; 25(1): 216-225. doi: 10.1093/annonc/mdt461

8. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemo radiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomized phase 3 trial. *Lancet Oncol*. 2013; 14(3): 257-264. doi: 10.1016/S1470-2045(13)70011-1

9. Budach W, Bölke E, Kammers K, et al. Induction chemotherapy

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-114

followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials. *Radiother Oncol*. 118(2): 238-243. doi: 10.1016/j.radonc.2015.10.014

10. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res*. 2002; 62: 7350-7356. Web site. http://cancerres.aacrjournals.org/content/62/24/7350.long. Accessed January 29, 2016.

11. Masui H, Kawamoto T, Sato JD, Wolf B, Sato G, Mendelsohn J. Growth inhibition of human tumor cells in athymic mice by anti-epidermal growth factor receptor monoclonal antibodies. *Cancer Res*. 1984; 44(3): 1002-1007. Web site. http://cancerres.aacrjournals.org/content/44/3/1002.long. Accessed January 29, 2016.

12. Mendelsohn J. Growth factor receptors as targets for anti-tumor therapy with Monoclonal antibodies. *Prog Allergy*. 1988; 45: 147-160.

13. Balaban N, Moni J, Shannon M, Dang L, Murphy E, Goldkorn T. The effect of ionizing radiation on signal transduction: Antibodies to EGF receptor sensitize A431 cells to radiation. *Biochim Biophys Acta*. 1996; 1314: 147-156.

14. Schmidt-Ullrich RK, Mikkelsen RB, Dent P, et al. Radiation-induced proliferation of the human A431 squamous carcinoma cells is dependent on EGFR tyrosine phosphorylation. *Oncogene*. 1997; 15: 1191-1197. Web site. http://www.nature.com/onc/journal/v15/n10/abs/1201275a.html Accessed January 29, 2016.

15. Tan EH, Goh C, Lim WT, et al. Gefitinib, cisplatin, and concurrent radiotherapy For locally advanced head and neck cancer: EGFR FISH, protein expression, and Mutational status is not predictive biomarkers. *Ann Oncol*. 2012; 23(4): 1010-1016. doi: 10.1093/annonc/mdr327

16. Harrington K, Berrier A, Robinson M, et al. Randomized Phase II study of oral lapatinib combined with chemo radiotherapy in patients with advanced Squamous cell carcinoma of the head and neck: rationale for future randomized Trials in human papilloma virus-negative disease. *Eur J Cancer*. 2013; 49(7): 1609-1618. doi: 10.1016/j.ejca.2012.11.023

17. Martins RG, Parvathaneni, Bauman JE, et al. Cisplatin and radiotherapy with or without erlotinib in locally advanced squamous cell carcinoma of the head and neck: a randomized phase II trial. *J ClinOncol*. 2013; 31(11): 1415-1421. doi: 10.1200/JCO.2012.46.3299

18. Reddy BK Lokesh V, Vidyasagar MS, et al. Nimotuzumab provides survival Benefit to patients with inoperable advanced squamous cell carcinoma of the Head and Neck: a randomized, open-label, phase II, 5-year study in Indian patients. *Oral Oncol*. 2014; 50(5): 498-505. doi: 10.1016/j.oraloncology.2013.11.008

19. Mesía R, Henke M, Fortin A, et al. Chemo radiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the Head and neck (CONCERT-1): a randomized, controlled, open-label phase 2 trial. *Lancet Oncol*. 2015; 16(2): 208-220. doi: 10.1016/S1470-2045(14)71198-2

20. 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. doi: 10.1056/NEJMoa053422

21. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for loco regionally advanced head and neck cancer: 5-year survival data from a phase 3 randomized trial and relation between cetuximab induced rash and survival. *Lancet Oncol*. 2010; 11: 21-28. doi: 10.1016/S1470-2045(09)70311-0

22. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent Accelerated Radiation PlusCisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. 2014; 8(25): 2940-2950; doi: 10.1200/JCO.2013.53.5633

23. Siu LL, Waldron JN, Chen BE, et al. Phase III randomized trial of standard fractionation radiotherapy (SFX) with concurrent cisplatin (CIS) versus accelerated fractionation radiotherapy (AFX) with panitumumab (PMab) in patients (pts) with loco regionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): NCIC Clinical Trials Group HN.6 trial. *J Clin Oncol*. 2015; (suppl; abstr 6000).

24. Trotti A. Phase III Trial of Radiotherapy plus Cetuximab versus Chemoradiotherapy in Hpv-Associated Oropharynx Cancer, RTOG 1016. *J Clin Oncol*. 2014; 32:5s-32:5s.

25. Tupchong L, Scott CB, Blitzer PH, et al. Randomized study of preoperative versus Postoperative radiation therapy in advanced head and neck carcinoma: Long-term follow-up of RTOG study 73-03. *Int J Radiat Oncol Biol Phys*. 1991; 20: 21-28. doi: 10.1016/0360-3016(91)90133-O

26. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative Radiation therapy of head and neck cancer: First report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys*. 1993; 26: 3-11. doi: 10.1016/0360-3016(93)90167-T

27. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 2012; 84(5):1198-1205. doi: 10.1016/j.ijrobp.2012.05.008

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-3-114

28. Bernie J. Postoperative Irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004; 350(19): 1945-1952. doi: 10.1056/NEJMoa032641

29. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck*. 2005; 27: 843-850. doi: 10.1002/hed.20279

30. Machtay M. A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer. RTOG 0920 clinical trials.gov, NCT00956007. Web site. https://clinicaltrials.gov/ct2/show/NCT00956007. Accessed January 29, 2016.

31. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol*. 2014; 32(23): 2486-2495. doi: 10.1200/JCO.2013.53.9163

32. Harrington KJ, Temam S, D'Cruz A, et al. Final analysis: A randomized, blinded, placebo (P)-controlled phase III study of adjuvant postoperative lapatinib (L) with concurrent chemotherapy and radiation therapy (CH-RT) in high-risk patients with squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol*. 2014; 32: 5s (suppl; abstr 6005).

33. Soo KC, Tan EH. Phase III, double-blind, placebo-controlled study of post-operative adjuvant concurrent chemo-radiotherapy with or without nimotuzumab for stage III/IV head and neck squamous cell cancer. Clinical trials.gov NCT00957086. Web site. https://clinicaltrials.gov/ct2/show/NCT00957086. Accessed January 29, 2016.