Cetuximab Plus Cisplatin, Irinotecan, and Thoracic Radiotherapy as Definitive Treatment for Locally Advanced, Unresectable Esophageal Cancer

A Phase-II Study of The SWOG (S0414)

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Introduction: The specific aims of the study were to evaluate the 2-year overall survival (OS) and progression-free survival (PFS), toxicity profile, and best objective response rate in patients with locally advanced, clinically unresectable esophageal cancer receiving cetuximab, cisplatin, irinotecan, and thoracic radiotherapy (TRT) within a multi-institutional cooperative-group setting.

Methods: Eligible patients (cT4 M0 or medically unresectable, biopsy proven, and noncervical esophageal cancer) were to receive four 21-day cycles of cetuximab 400 mg/m^2 (day 1, cycle 1), cetuximab 250 mg/m^2 (day 8, 15, cycle 1; then days 1, 8, and 15 for subsequent cycles), cisplatin 30 mg/m^2 (days 1 and 8, all cycles), and irinotecan 65 mg/m^2 (days 1 and 8, all cycles). TRT was administered at 1.8 Gy in 28 daily fractions to a total dose of 50.4 Gy, to begin with on day 1 of cycle 3. The primary endpoint was 2-year OS, with an accrual goal of 75 patients with adenocarcinoma.

Results: The study was closed because of slow accrual, with 21 eligible patients (11 squamous, 10 adenocarcinoma) enrolled from May 2005 to September 2007. Two-year OS and PFS (95% confidence interval [CI]) were 33.3% (14.6–57.0%) and 23.8% (8.2–47.2%), respectively. Kaplan–Meier estimates of median (95% CI) OS and PFS were 11.2 (6.4–43.6) and 6.4 (3.7–12.0) months, respectively. The overall response rate (95% CI) among 17 evaluable patients was 17.6% (3.8–43.4%), including 6% confirmed complete responders and 12% unconfirmed partial responders. Two deaths resulted from protocol treatment (sudden death and gastrointestinal necrosis). Ten (47.6%) and 6 (28.6%) patients had grade-3 or -4 toxicity, respectively: 52.4% were hematologic, 23.8% had fatigue, 19.0% had nausea, 19.0% had dehydration, and 19.0% had anorexia.

Conclusions: Concomitant cetuximab, cisplatin, irinotecan, and TRT were poorly tolerated in the first North American cooperative group trial testing this regimen for locally advanced esophageal cancer as treatment-related mortality approached 10%. Single-institution phase-II cetuximab-based combined modality trials have yielded encouraging results in preliminary analyses. The SWOG GI Committee endorses enrollment to open clinical trials to clarify the therapeutic ratio of cetuximab-based combined modality approaches for esophageal cancer.

Key Words: Esophageal, Cetuximab, Cisplatin, Irinotecan, Radiotherapy.

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An estimated 17,460 new cases of esophageal cancer will be diagnosed in the United States in 2012, accompanied by 15,070 deaths from the disease.[1] It is the fifth leading cause of cancer deaths in men over the age of 40 years. The National Comprehensive Cancer Network guidelines recommend the concomitant administration of cisplatin, 5-fluorouracil (5-FU), and thoracic radiotherapy (TRT) as definitive therapy for patients with locally advanced esophageal cancer. Both cisplatin and 5-FU have proven to be relatively effective radiosensitizing agents in preclinical and clinical experience over the past two decades. Radiation Therapy Oncology Group (RTOG) 85-01 demonstrated a 27% 5-year survival compared to 0% for patients receiving the combined-modality regimen over TRT (6400 cGy) alone.[2,3] Despite the addition of systemic cytotoxic agents to TRT, local failure within the gross tumor volume (GTV) remains

the most common cause of treatment failure.[4] A Patterns of Care analysis by the American College of Radiology for the period of 1996–1999 suggests that 56% of patients with esophageal cancer receive combined-modality therapy as definitive therapy.[5] Infusional 5-FU delivered over several days can be cumbersome and the toxicity profile may be so profound as to preclude an adequate number of courses, despite its efficacy. Thus, there is a pressing need for effective, less toxic, and novel treatment programs for patients with locally advanced esophageal cancer.[6]

Irinotecan, a topoisomerase-I enzyme inhibitor, is a semisynthetic, water-soluble derivative of the plant *Camtotheca acuminata* and inhibits topo-1, a nuclear enzyme, via binding and stabilization of the topo-1/DNA cleavable complex.[7] A 22% objective response rate in advanced esophageal and gastric cancer has been reported, using irinotecan combined with a 5-FU/folinic acid backbone.[8] This study and other irinotecan-based studies (408 total combined patients) on esophageal and gastric cancer suggest response rates of 14% to 65%.[7,9–15]

In vitro and in vivo data suggest that irinotecan exhibits significant radiosensitizing properties.[16–20] Phase-I experience with single-agent irinotecan and TRT noted that 60 mg/m^2 weekly for 5 to 6 weeks could be safely administered in a combined-modality setting.[21] On the basis of published phase-II experience of weekly irinotecan and cisplatin for advanced esophageal cancer that demonstrated a 57% overall response rate (including two clinical complete responses) along with a nearly 15-month median actuarial survival, investigators added TRT to this regimen for patients with stage-II or -III lesions.[12] A dose-escalation study of weekly irinotecan, fixed-dose cisplatin, and TRT after 4 weeks of induction therapy (irinotecan 65 mg/m^2 weekly and cisplatin 30 mg/m^2 weekly), determined that the maximum tolerated dose of irinotecan was 65 mg/m^2 weekly for 5 weeks.[22] TRT was administered at 5040 cGy in standard 180 cGy fractions. This combination of non-5-FU-based chemoradiotherapy was shown to be safe and therapeutically active against primary esophageal cancer. Moreover, the pathologic complete response rate of 32% was consistent with prior results in the literature that included infusional fluorinated pyrimidine-based chemoradiotherapy. The same group recently reported the results of a phase-II study of induction weekly irinotecan and cisplatin followed by the same regimen concurrent with TRT to 5040 cGy, followed by surgery.[23] R0 resection was obtained in 69% of the patients, and the pathologic complete response rate was 16%. Postinduction positron emission tomography response was correlated with better clinical outcomes. A retrospective analysis of induction cisplatin and irinotecan followed by concurrent cisplatin, irinotecan, and TRT with a median follow-up of 2 years reported a 2-year OS of 42% and acceptable tolerability of this regimen.[24]

Cetuximab is a novel chimeric monoclonal antibody directed against the external domain of the epidermal growth factor receptor (EGFR). This agent is able to inhibit the activity of tyrosine kinase on the inner surface of the cell membrane. This results in inhibition of downstream events within the signal transduction cascade from the cell surface to the nucleus. Preclinical data suggest that cetuximab has radiosensitizing properties.[25] Its utility combined with radiotherapy has been demonstrated for squamous-cell carcinoma of the head and neck.[26] Cetuximab has been safely used in combination with cisplatin[27,28] and with irinotecan,[29,30] and evidence suggests that cetuximab acts to enhance irinotecan's cytotoxic properties by down-regulating EGFR pathways the topoisomerase inhibitor is known to up-regulate.[31]

Consequently, a novel form of antitumor activity may occur to support this study's hypotheses that:

1. As definitive therapy for primary locally advanced and clinically unresectable esophageal cancer, cetuximab, in combination with cisplatin, irinotecan, and TRT will produce a favorable response rate and survival.
2. In combination with cisplatin, irinotecan, and TRT, cetuximab will cause significantly less clinical toxicity than 5-FU-based chemoradiotherapy, a current standard of care for patients receiving either neoadjuvant or definitive combined-modality therapy for esophageal cancer. Cisplatin and irinotecan can be administered in full doses when given with cetuximab.
3. Patients with primary esophageal tumors expressing low levels of ERCC-1 and high levels of EGFR will exhibit an encouraging progression-free survival (PFS) and clinical complete response rate after definitive treatment with cetuximab, cisplatin, irinotecan, and external beam radiation.

PATIENTS AND METHODS

Patients with pathologically documented squamous-cell carcinoma or adenocarcinoma of the thoracic esophagus (≥20 cm from the incisors) or of gastroesophageal junction were considered eligible, and all had measurable or evaluable cT4 M0 or unresectable disease. History, physical examination, endoscopic ultrasound or esophagogastroduodenoscopy, chest radiography, positron emission tomography scans with computed tomography or magnetic resonance imaging, and adequate renal and hepatic function, absence of prior cancer, absence of prior chemotherapy or radiotherapy, Zubrod performance status 0 to 2, and Institutional Review Board-approved informed consent were all required. A baseline electrocardiogram and pulmonary-function studies were recommended. Bronchoscopy with negative cytology was required for patients with a primary tumor less than 26 cm from the incisors. Patients with clinical evidence of tracheo-esophageal fistulas were ineligible for this trial.

Induction Chemotherapy

Two cycles of cetuximab 400 mg/m^2 intravenous (IV) loading dose on day 1 followed by 250 mg/m^2 (days 18, 15; and days 22, 29, and 36), cisplatin 30 mg/m^2 IV bolus (days 1, 8; and days 22, 29), and irinotecan 65 mg/m^2 (days 1, 8; and days 22, 29) combination chemotherapy were administered. Cisplatin was administered after adequate hydration. Cetuximab was provided courtesy of ImClone, a wholly owned subsidiary of Eli Lilly and Co. (Indianapolis, IN), and Bristol-Myers-Squibb (New York, NY). Standard pretreatment agents were administered.

Concurrent Chemotherapy

Following the completion of induction chemotherapy, concurrent chemoradiotherapy was initiated with the first fraction

of TRT. Concurrent systemic therapy consisted of two cycles of cetuximab 250 mg/m^2 IV (days 43, 50, and 57; 64, 71, and 78), cisplatin 30 mg/m^2 IV (days 43, 50; and 64, 71), and irinotecan 65 mg/m^2 IV (days 43, 50; and 64, 71).

Radiotherapy

Three-dimensional-conformal megavoltage radiotherapy (IMRT was not allowed) was administered at 1.8 Gy in 28 daily fractions (excluding weekends and holidays) to a total dose of 50.4 Gy, timed to begin concurrently with chemotherapy. The GTV included the primary tumor mass and involved lymph nodes. This GTV included the celiac nodal region in patients with tumor in the distal third of the esophagus. A clinical target volume (CTV) was derived by expanding the GTV 5 cm superiorly and inferiorly for the primary tumor, and at least 2 cm around any involved lymph nodes. For patients with tumor extending at least 2 cm above the carina, the CTV included the supraclavicular nodal regions. Margins for expansion to the planning target volume were left to the discretion of the treating radiation oncologist. Heterogeneity corrections were applied, and at least 95% of the CTV received the prescribed dose. All TRT plans were centrally reviewed by the Quality Assurance Review Center (Providence, RI) for compliance with the study parameters.

Growth Factor Support

The use of granulocyte-colony stimulating factor was permitted only for patients who developed grade 3 or 4 neutropenia. Granulocyte-colony stimulating factor was not permitted for primary prevention of neutropenia.

Dose Modifications

No dose modifications for radiotherapy were allowed. A hemogram was performed before systemic therapy on each infusion day. Irinotecan was to be held for white blood count less than 3000/ul, absolute neutrophil count less than 1000/ul, or platelets <less than 100,000/ul; for febrile neutropenia or bleeding complications; for grade-2+ mucositis or diarrhea; or for grade-4 fatigue lasting more than 3 days. Cisplatin was dose reduced for a moderate increase in creatinine but was omitted for creatinine more than 2.0 mg/dl, permanently discontinued for grade-3+ peripheral neuropathy, and dose reduced by 25% for other grade-3+ nonhematologic toxicity. Cetuximab was discontinued for grade-4 acneiform rash; it was delayed and its dose was potentially reduced for grade-3 rash, but no dose modifications were made for grade-1 or -2 rash. Grade-1 or -2 infusion reaction from cetuximab was an indication for a permanent 50% dose reduction; Grade-3 or -4 infusion reactions led to permanent discontinuation of the drug. All patients were prophylactically treated with oral tetracycline and topical clindamycin.

Assessment of Response

The objective response was evaluated according to the response evaluation criteria in solid tumors criteria. All toxicities were scored according to the CTCAE, version 3.0 (NCI Common Terminology Criteria for Adverse Events).

Statistical Methods

The main objective of the study was to assess the 2-year overall survival (OS) of this novel therapeutic combination. This primary endpoint was driven by accrual of patients with adenocarcinoma, although up to 25 patients with squamous-cell tumors were eligible for enrollment. The regimen was to be considered promising if the true OS at 2 years was at least 50%, but not of further interest if the true survival rate was less than 35%. With a planned 75 adenocarcinoma patients, the power of a one-sided 0.05 level test to detect a 35% versus a 50% 2-year OS was 0.91. Additional endpoints included assessment of the toxicity profile of this regimen, best objective response to therapy, and PFS.

RESULTS

The study was closed because of slow accrual, with only 22 patients enrolled from May 2005 to September 2007. One patient was ineligible because of involvement of the cervical esophagus. The baseline characteristics of the 21 eligible patients are described in Table 1. The median age was 61 years (range, 43–83 years).

Toxicities

Toxicity data for the 21 eligible patients are presented in Table 2. Eighteen patients (85.7%) exhibited a maximum grade-3 or higher toxicity. Of the eight patients (38.1%) experiencing grade-4 or higher toxicity, five had squamous-cell and three had adenocarcinoma histology. Treatment-related mortality was observed in two patients (9.5%, sudden death and gastrointestinal necrosis), both of whom has squamous-cell histology. In both cases, the treating physician felt that protocol treatment may have been a contributing factor. The most common grade-3 or higher toxicities were leukopenia (42.9%), neutropenia (28.6%), fatigue (23.8%), lymphopenia (19.0%), dehydration (19.0%), and gastrointestinal complaints (diarrhea [23.8%], nausea [19.0%], and anorexia [19.0%]). Febrile neutropenia was seen in fewer than 5% of the patients. Eighteen patients (85.7%) were able to complete treatment as planned (two deaths, one stopped because of side effects).

TABLE 1. Baseline patient characteristics/demographics (N = 21)

Age	
Median	61.4 (43–83)
Sex	
Male	15 (71%)
Female	6 (29%)
Race	
Caucasian	15 (71%)
African-American	4 (19%)
Asian	2 (10%)
Histology	
Adenocarcinoma	10 (48%)
Squamous cell	11 (52%)

TABLE 2. Maximum Grade of Adverse Events by Category (Maximum Grade Experienced by Patient for Each Category) (N = 21)

Grade	3 (%)	4 (%)	5 (%)
Hematologic			
Anemia	14.3	—	—
Leukopenia	33.3	9.5	—
Lymphopenia	9.5	9.5	—
Neutropenia	14.3	14.3	—
Neutropenia, febrile	4.8	—	—
Nonhematologic			
Acneiform rash	4.8	—	—
Anorexia	19.0	—	—
CNS ischemia	—	4.8	—
Creatinine	—	4.8	—
Dehydration	19.0	—	—
Diarrhea	23.8	—	—
Dysphagia	14.3	—	—
Esophagitis	9.5	—	—
Fatigue	23.8	—	—
GI necrosis	—	—	4.8
GI pain: abdomen	4.8	—	—
GI pain: esophagus	4.8	—	—
GI perforation: colon	4.8	—	—
Hyperglycemia	4.8	—	—
Hypoalbuminemia	4.8	—	—
Hypocalcemia	4.8	—	—
Hypokalemia	9.5	—	—
Hypomagnesemia	4.8	—	—
Hyponatremia	4.8	—	—
Nausea	19.0	—	—
Neuropathy	4.8	—	—
Renal failure	—	4.8	—
Skin lesions	4.8	—	—
Sudden death	—	—	4.8
Thrombosis/embolism	—	4.8	—
Typhlitis	—	4.8	—
Vomiting	14.3	—	—
Weight loss	4.8	—	—

CNS, central nervous system; GI, gastrointestinal.

Response

Objective responses were assessed by the investigators at the treating institution using response evaluation criteria in solid tumors criteria; 17 were evaluable. The overall response rate was 17.6% (95% confidence interval [CI]: 3.8–43.4%), including one complete response (5.9%) and two unconfirmed partial responses (11.8%). All responders had squamous-cell histology. Three patients (17.6%) exhibited stable disease, four (23.5%) had progressive disease, and six (35.3%) with inadequate assessment were considered nonresponders. These results are summarized in Table 3.

Survival

With over 3.5 years of follow-up among those last known alive, the median (95% CI) OS was 11.2 months (range, 6.4–43.6 months). The median (95% CI) PFS was 6.4 months (range, 3.7–12.0 months). Two-year OS and PFS is 33.3% (95% CI: 14.6–57.0%) and 23.8% (95% CI: 8.2–47.2%), respectively. Two-year OS (95% CI) within the 11 patients with squamous-cell histology and the 10 patients with adenocarcinoma is 45.5% (16.0–74.9%) and 20.0% (0.0–44.8%), respectively. Kaplan–Meier curves for overall and PFS for the entire study population are shown in Figures 1 and 2, respectively.

TABLE 3. Best Objective Response by Response Evaluation Criteria in Solid Tumors Criteria (N = 17 Measurable)

	Total	
Complete response	1	6%
Unconfirmed partial response	2	12%
Stable/No response	3	18%
Progressive disease	4	24%
Symptomatic deterioration	1	6%
Assessment inadequate	6	35%
Total	17	100%

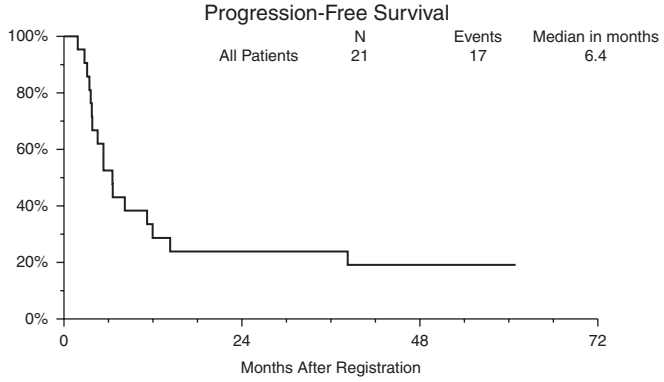

FIGURE 1. Kaplan-Meier curve of overall survival (OS) in SWOG S0414.

DISCUSSION

The long-term results of RTOG 85-01 suggest that one of four good-performance patients with locally advanced esophageal cancer, who are able to successfully receive concomitant chemoradiotherapy will be alive at the 5-year mark.[3] Patients with clinically T4 primary esophageal cancers often have suboptimal performance status, in part, because of the symptoms consistent with the invasion of adjacent structures,[32] although preoperative combined modality approaches have been reported with variable success.[33,34]

Building on the platform of RTOG 85-01, investigators have attempted to both increase the intensity of treatment by adding surgery (trimodality) often after preoperative combined modality therapy, and by adding full-dose systemic therapy. Strategic induction approaches allow both the opportunity of administering full-dose systemic therapy and serving as an in-vivo assessment of response with novel systemic therapeutics before the administration of a

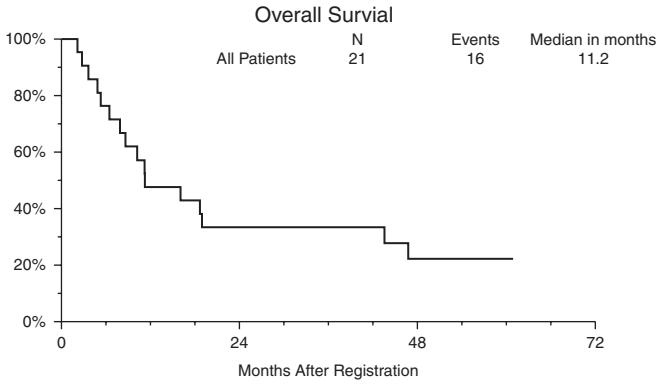

FIGURE 2. Kaplan-Meier curve of progression-free survival (PFS) in SWOG S0414.

concomitant chemoradiotherapy platform. Several investigators have successfully tested induction systemic combination chemotherapy and/or molecular targeted therapeutics, before concomitant chemotherapy.[35]

One of the combination cytotoxic chemotherapy regimens upon which the present study was based included irinotecan and cisplatin. This doublet yielded encouraging objective responses, including some clinical complete responses, in patients with unresectable or metastatic esophageal cancer.[12,13] Furthermore, a phase-1 trial of weekly irinotecan and cisplatin plus concomitant TRT by an experienced group of investigators noted an acceptable toxicity profile along with encouraging observations of symptomatic improvement and objective responses.[21] A phase-II trial by the MD Anderson Cancer Center group modified this regimen by first administering induction irinotecan and cisplatin for one or two cycles followed by chemoradiotherapy using a 5-FU, paclitaxel, TRT backbone before surgery for patients with clinically resectable disease.[36] More recently, the Spanish Cooperative Group for Digestive Tumor Therapy's phase II trial that included induction irinotecan and cisplatin followed by concomitant chemoradiotherapy with the same two drugs before surgical resection, noted acceptable toxicity and modest activity compared to the historical published experience of cisplatin, 5-FU, and TRT in patients with clinically resectable disease.[37] When this study group and others tested this regimen in patients with clinically unresectable disease, the results were even less favorable.[22,38]

Over the past decade, there has been significant progress in characterizing mechanisms of tumor growth that result from altered regulation of various parts of the signal-transduction pathway. At the turn of the century the EGFR, a member of the ErbB family of growth-factor receptor tyrosine kinases, was reported to be overexpressed in a number of epithelial tumors of the upper aerodigestive tract, including esophageal cancer, hence suggesting a target that could be used to make progress with this difficult-to-treat solid tumor.[39,40] Midway during the decade the concomitant administration of the chimeric monoclonal antibody against the EGFR, cetuximab, and ionizing radiation was shown to yield a superior survival outcome in patients with head and neck cancer.[23,24]

On the basis of encouraging preclinical and clinical data cetuximab and ionizing radiation, and the phase-I/II results of irinotecan–cisplatin and TRT in 2004 SWOG, a federally funded cancer research group, designed a phase-II clinical trial for esophageal-cancer patients. SWOG-0414 is the first U.S. multi-institutional, prospective, cooperative-group trial incorporating the novel combination of cetuximab, cisplatin, and irinotecan in patients with locally advanced or unresectable esophageal cancer. This regimen was poorly tolerated, with 38% of patients experiencing grade-4 or -5 toxicities and a treatment-related mortality approaching 10%. The objective response rate was disappointing, with only one CR and two unconfirmed PRs to therapy, all among patients with squamous-cell histology.

No patients in this study experienced grade-3 or higher pulmonary toxicity. This is in contrast to the recently reported results of Eastern Cooperative Oncology Group 2205, a phase-II study examining the addition of cetuximab to concurrent oxaliplatin, 5-FU, and 45 Gy TRT delivered as neoadjuvant therapy before surgery for patients with resectable adenocarcinoma of the esophagus.[41] Despite a promising pathologic CR rate, four out of 22 patients died from ARDS postoperatively, compared to no incidence of ARDS in ECOG 1201 without cetuximab. Other reports of concurrent chemoradiation for esophageal cancer using cetuximab have not shown significant pulmonary toxicity.[42,43]

This trial was closed because of slow accrual. A potential confounding factor is that SWOG sites were concurrently accruing to SWOG-0356, a protocol for resectable esophageal adenocarcinoma. Patients with technically resectable cT4 disease may have preferentially been enrolled on SWOG-0356, skewing the population to the medically unresectable patients for this trial. This could also explain the poor accrual for adenocarcinomas and the fact that the majority of patients enrolled on this trial had squamous tumors. Furthermore, we may have chosen a suboptimal doublet to combined with TRT, as others have reported superior tolerability with a carboplatin–paclitaxel backbone during concomitant therapy.[33,39,44] In addition, investigators have recently shown that the actual expression of EGFR may range from low to nonexistent for esophageal adenocarcinomas.[45]

Given the unfavorable results of this trial, we would not recommend further development of this particular regimen for patients with locally advanced or medically unresectable esophageal cancer. Several other studies in esophageal and non–small-cell lung cancer have shown safe and effective combination of cetuximab and radiotherapy, and we believe that alternative cetuximab-based chemoradiotherapy regimens may hold promise for esophageal cancer.[39,40,46] Although recent reports of combining chemoradiotherapy with oral tyrosine kinase inhibitors against EGFR, such as erlotinib, demonstrate feasibility, we believe that significant dysphagia will likely result in noncompliance in a prospective, multi-institutional trial for patients with advanced esophageal cancer.[47,48] The RTOG is currently conducting a phase-III trial examining the addition of cetuximab to paclitaxel, cisplatin, and TRT for unresectable esophageal cancer, and we would encourage enrollment to this pivotal trial. In addition to this,, the SCOPE1 trial in the United Kingdom is currently open

to accrual.[49] This multicenter phase-II/III study randomizes patients with locally advanced esophageal cancer to induction cisplatin and capecitabine followed by the same regimen concurrent with TRT (5000 cGy in 200 cGy fractions) versus the investigational arm that simply adds cetuximab to the induction and concurrent chemotherapy of the control arm. The results of these two randomized trials will help to answer the question of the role of cetuximab in this patient population.

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