ORIGINAL ARTICLE

DOCETAXEL, CISPLATIN, AND FLUOROURACIL INDUCTION CHEMOTHERAPY FOLLOWED BY ACCELERATED FRACTIONATION/CONCOMITANT BOOST RADIATION AND CONCURRENT CISPLATIN IN PATIENTS WITH ADVANCED SQUAMOUS CELL HEAD AND NECK CANCER: A SOUTHWEST ONCOLOGY GROUP PHASE II TRIAL (S0216)

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Abstract: *Background.* In an effort to optimize nonoperative therapy in patients with locoregionally advanced head and neck squamous cell cancer, the Southwest Oncology Group conducted a phase II trial combining 3-drug taxane-containing induction chemotherapy with accelerated fractionation/concomitant boost radiation and concomitant single-agent cisplatin.

Methods. Two induction courses using docetaxel (75 mg/m^2 on day 1), cisplatin (100 mg/m^2 on day 1), and fluorouracil (1000 mg/m^2/day continuous intravenous infusion days 1–4) were given, with an interval of 21 days. Patients who were stable or responded to the chemotherapy received definitive accelerated fractionation/concomitant boost radiation with concurrent cisplatin (100 mg/m^2) on days 1 and 22 of radiation.

Results. There were 74 eligible and evaluable patients enrolled between March 1, 2003, and August 15, 2004; 52 (70%) had stage IV disease. At least 1 grade 3-4 toxicity was experienced by 63 patients (85%) during induction. A total of 61 patients completed induction and began concurrent chemoradiotherapy; 50 (68%) completed all planned treatment. At least 1 grade 3-4 toxicity was noted in 53 of the 58 patients (91%) evaluated for toxicity from concurrent chemoradiotherapy. Two patients died during induction, and 2 during chemoradiation. With a median follow-up of 36 months (range, 14–50), the 2-year and 3-year overall survival estimates were 70% and 64%,

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with 2-year and 3-year progression-free survival estimates of 66% and 61%, respectively.

Conclusions. Three-drug induction chemotherapy followed by accelerated fractionation/concomitant boost radiation and concurrent cisplatin is toxic but feasible within a cooperative group. In this patient cohort with advanced head and neck squamous cell cancer, overall and progression-free survivals were encouraging, justifying further study of this approach. © 2009 Wiley Periodicals, Inc. *Head Neck* **32:** 221–228, 2010

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Multiple studies of both single-agent and combination chemotherapy administered with concomitant definitive radiation have now been reported and have demonstrated a clear survival and locoregional control benefit when compared with radiation therapy alone.[1] The best studied concurrent chemoradiotherapy regimen is radiation and single-agent cisplatin, which has been well established as a standard of care in the management of patients with unresectable head and neck cancer,[2] nasopharyngeal cancer,[3] and in postoperative patients with poor prognostic features.[4–6] It has also been proven to be the most successful strategy for nonoperative larynx preservation.[7] These conclusions have been confirmed and strengthened by the results of the large meta-analysis of chemotherapy on head and neck cancer (MACH-NC), which reported a 5-year 8% overall survival benefit ($p < .0001$) with concurrent chemoradiotherapy regimens when compared with radiotherapy alone.[8,9]

Along with the improved survival and locoregional control that has resulted from these aggressive concomitant treatment schedules has been an apparent shift in the pattern of treatment failure. Historically, locoregional disease control has been the most important concern in disease management. Distant metastases were a relatively uncommon event. Recently, several single-institution phase II trials of aggressive concurrent chemoradiotherapy and altered fractionation radiation have reported locoregional control rates in excess of 90%, with distant metastases representing the most frequent cause of treatment failure.[10,11] This observation has suggested a possible role for additional systemic chemotherapy in an effort to improve overall treatment success by decreasing this incidence of distant recurrence.[12,13] Given the difficulties associated with the administration of adjuvant chemotherapy after completion of definitive chemoradiotherapy, re-exploration of the use of induction therapy would seem to be reasonable.

Induction therapy is hardly a new concept in the treatment of head and neck cancer. A large number of phase III studies have been conducted comparing induction chemotherapy followed by definitive surgery and/or radiation to definitive management alone. Response rates as high as 90% using well-established treatment regimens have been reported.[13] Although individual studies have failed to demonstrate any consistent improvement in locoregional control or survival, meta-analysis has been able to identify a small survival benefit (hazard ratio 0.88, 95% CI: 0.79–0.97) for induction regimens containing fluorouracil and a platin, the most widely tested chemotherapy combination used in this setting.[8] In several of these induction chemotherapy trials it was also noted that distant metastases were reduced in those patients who received chemotherapy.[14–16] Thus, the argument can be made that the sequential use of aggressive multiagent induction therapy followed by optimal definitive chemoradiotherapy may successfully improve both locoregional and distant control and further improve overall survival.[13,17]

Recent work has produced evidence that the incorporation of a taxane, either paclitaxel or docetaxel, into the well-tested fluorouracil and cisplatin combination can produce additional benefit. Hitt et al,[18] Vermorken et al,[19] and Posner et al[20] have reported results from 3 separate phase III studies comparing induction fluorouracil and cisplatin with induction fluorouracil, cisplatin, and a taxane followed by definitive therapy. Improvements in overall response rate, complete response rate, organ preservation, and survival were reported. Thus, a 3-drug combination of fluorouracil, cisplatin, and either paclitaxel or docetaxel can be considered to be the most effective induction chemotherapy combination for this disease, and, as such, would be the appropriate choice for this kind of sequential treatment regimen.

The optimal radiation therapy fractionation schedule has also been an unresolved question for many years. The results from a large Radiation Therapy Oncology Group trial (RTOG 9003) and other phase III studies appear to demonstrate a locoregional control benefit from altered fractionation treatment schedules when compared with conventional once-daily treatment.[21]

Meta-analysis has confirmed this conclusion.[22] Although the best altered fractionation approach is yet undefined, RTOG 9003 suggested a benefit from the accelerated fractionation/concomitant boost treatment schedule.

The hypothesis behind this phase II Southwest Oncology Group trial was that optimal nonoperative therapy should address both locoregional control and distant metastases and should therefore sequentially employ the most effective multimodality components available to achieve each of these ends. An induction taxane, fluorouracil, and cisplatin combination chemotherapy regimen was chosen followed by concurrent chemoradiotherapy using single-agent cisplatin and altered fractionation radiation therapy with the accelerated fractionation concomitant boost schedule. We chose to give only 2 cycles of induction chemotherapy, rather than the 3[18,20] or 4[19] cycles used by previous investigators, because of concern about the potential for cumulative cisplatin neurotoxicity.

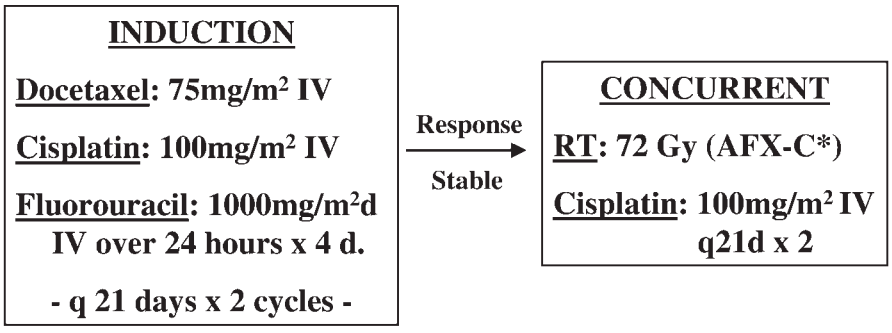
The objectives of this trial were to (1) assess the overall survival in patients with advanced head and neck squamous cell cancer treated with this multimodality treatment regimen; (2) estimate the clinical complete response rate after both induction therapy and concomitant chemoradiotherapy; and (3) evaluate the toxicities of induction chemotherapy and of this entire multimodality treatment approach.

PATIENTS AND METHODS

Enrollment on this trial required the diagnosis of a previously untreated stage III or IV (M0) head and neck squamous cell cancer with an identified primary site excluding the lip, nasopharynx, paranasal sinus, or salivary gland. Patients were eligible if deemed appropriate for radiation therapy with curative intent. A Zubrod performance status of 0 or 1; adequate hematologic, renal, and hepatic function; and a chest radiograph that did not demonstrate any metastatic disease were also required. Pretreatment evaluation by radiation oncology, medical oncology, head and neck surgery and dentistry, and documentation of disease extent by either CT or MRI were mandated. Positron emission tomography scans were not routinely requested for this study. An examination under anesthesia was required if deemed necessary by the head and neck surgeon. Those patients with pre-existing peripheral neuropathy were excluded. Similarly, patients with any prior malignancy were also ineligible for this trial, excluding those with adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or adequately treated stage I or II cancer in remission for 5 years.

This study was conducted under the auspices of the Southwest Oncology Group and approved by the local institutional review boards of all participating institutions. Written informed consent, in accordance with institutional and federal guidelines, was required from all patients before entering this protocol.

The treatment schema is depicted in Figure 1. Treatment included induction chemotherapy followed by concurrent chemoradiotherapy. Induction chemotherapy utilized a 3-drug combination of intravenous docetaxel 75 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 1, and fluorouracil 1000 mg/m^2/day as a continuous 24-



RT:AFX-C; Radiation therapy: Accelerated fractionation/concomitant boost schedule. Total Volume: 54 Gy @ 1.8 Gy qd, Boost Volume: 18 Gy @ 1.5 Gy qd last 12 d.

FIGURE 1. S0216: treatment schema.

hour intravenous infusion for 4 days beginning on day 1. Two courses of this treatment regimen were given with an interval of 21 days. Patients received prophylactic ciprofloxacin for 10 days after chemotherapy administration and standard antiemetics, hydration, and diuresis.

Three weeks after completion of the second cycle of induction chemotherapy, a response assessment was made using the same technique performed to document baseline disease. An examination under anesthesia was not required at this time. Patients with stable or responding tumor were then treated with concurrent chemoradiotherapy. Patients with progressive disease during or after induction chemotherapy were considered for surgical resection, if possible, with appropriate postoperative radiation therapy. If surgery was not possible in these patients, chemoradiotherapy was administered as per the protocol.

Radiotherapy consisted of the RTOG-accelerated fractionation, concomitant boost schedule. Patients were given 54 Gy in 30 daily fractions, 5 days per week at 180 cGy per fraction to the total treatment volume. Concomitant with the last 12 treatments, a boost volume was treated with 18 Gy at a rate of 150 cGy per day. The total volume included the primary tumor, neck nodes, and all areas at risk for microscopic disease. Boost volume included the primary tumor with a 1.5-cm margin, and any clinically enlarged lymph nodes. A minimum of 6 hours was required between the radiation administration to the total volume and to the boost volume on the last 12 concomitant treatment days. Only megavoltage equipment was allowed, and the use of intensity-modulated radiation therapy was not permitted on this study. Maximum dose to the spinal cord was 45 Gy. Two doses of concurrent cisplatin 100 mg/m^2 were given on days 1 and 22 of the radiation therapy along with standard hydration and antiemetic therapy.

Between 8 and 12 weeks after the completion of concomitant chemoradiotherapy, all patients underwent a comprehensive clinical and radiological assessment of response. The response assessment was again based on the same technique used at baseline. Patients who achieved a complete response to concomitant chemoradiotherapy were followed up for disease recurrence. Surgical resection was considered after concomitant chemoradiotherapy for those patients with histologically confirmed residual or recurrent disease at the primary site. Neck dissection was considered for all patients with clinical evidence of residual neck node disease after chemoradiotherapy and for patients with N2 or greater disease at presentation irrespective of their clinical response.

Statistical Considerations. Based on the results reported from RTOG 9003,[21] it was assumed that this treatment approach would not warrant further study if the true 2-year overall survival probability was 45% or less. If, however, the true 2-year overall survival probability was at least 61%, it would be of considerable interest in the treatment of advanced head and neck cancer. With 60 eligible patients enrolled over 2 years and an additional 2 years of follow-up, the power of a 1-sided log-rank test to detect an increase in the 2-year survival from 45% to 61% was 83% with an alpha of 0.05. An observed 2-year survival probability of 58% or greater would be considered as sufficient evidence to justify further study of this treatment approach, provided other factors such as progression-free survival and toxicity also appeared favorable.

Response at the primary, in the neck, and overall were each documented separately after the completion of induction chemotherapy and again after the completion of concurrent chemoradiotherapy. Sixty patients would be sufficient to estimate each of these clinically complete response rates to within 13% (95% CI). Sixty patients would also be sufficient to estimate any toxicity rate to within 13% (95% CI). Any toxicity with at least a 5% chance of occurring was likely to be seen at least once with 95% probability.

Overall survival and progression-free survival estimates were calculated using the method of Kaplan–Meier.[23] The survival times were calculated from the date of registration (no more than 5 working days before the initiation of induction chemotherapy) to the date of death due to any cause. Patients last known to be alive were censored at date of last contact. Progression-free survival times were calculated from the date of registration to the date of first documentation of progression (as defined by the Response Evaluation Criteria in Solid Tumors [RECIST] group), symptomatic deterioration (global deterioration of health status requiring discontinuation of treatment), or death due to any cause. Patients who had not been observed experiencing 1 of these events were censored at the date of last contact.

Table 1. Patient characteristics ($n = 74$).

Characteristic	No. (%)
Sex	
Male	61 (82)
Female	13 (18)
Race	
White	57 (77)
African–American	15 (20)
Other	2 (3)
Performance status	
0	39 (53)
1	35 (47)
Primary site	
Oral cavity	6 (8)
Oropharynx	35 (47)
Larynx	24 (32)
Hypopharynx	9 (12)
Median age, y	54 (range, 37–75)

Table 2. Tumor (T) and nodal (N) distribution ($n = 74$).

N classification	No. of patients by T classification					Total no. of patients
	T1	T2	T3	T4a	T4b	
N0			7	2	0	9
N1	2	4	9	3	0	18
N2a	0	2	4	0	0	6
N2b	1	3	7	5	1	17
N2c	2	4	2	6	3	17
N3	3	1	2	1	0	7
Total	8	14	31	17	4	74

RESULTS

Between March 1, 2003, and August 15, 2004, 76 patients were enrolled in this clinical trial. Two of these patients were deemed ineligible because of the presence of metastatic disease at entry, leaving 74 eligible and evaluable patients. Forty-one of these patients were from 7 member institutions of the Southwest Oncology Group. Thirty-five of these patients were from 15 different community affiliates of the Southwest Oncology Group member institutions.

The patient characteristics are shown in Table 1. Tumor and nodal disease extent based on the 6th edition of the American Joint Committee Cancer Staging Manual[24] is shown in Table 2. Overall, 70% of patients had stage IV disease, 15% with stage IVB tumors.

Patient accounting is detailed in Figure 2. Of the 74 eligible patients who began induction chemotherapy, 68 (92%) completed it. Sixty-one of these 68 patients (or 82% of the original 74) began concurrent chemoradiotherapy, all but 1 within 3 to 4 weeks of induction chemotherapy as specified by the protocol. Fifty patients (or 68% of the original 74) finished both induction cycles and all planned radiation. Both concurrent chemotherapy doses could be given to 45 of these 50 patients. The reasons for premature treatment discontinuation are indicated in the figure and were related to the treatment toxicity in 14 patients. Five patients were taken off study because of progressive disease during therapy. No statistically significant differences in patient or tumor characteristics could be identified between the 50 patients who completed their treatment and the 24 who did not.

Table 3 details the acute toxicity experienced by the 74 patients who underwent induction therapy. Grade 3-4 neutropenia was experienced by 59% of patients, and 18% required hospitalization for neutropenic fever. There were 2 toxic deaths, 1 due to febrile neutropenia and 1 from a cardiac cause. Overall, at least 1 grade 3 or greater toxicity occurred in 85% of patients. Table 3 also details the acute toxicity during

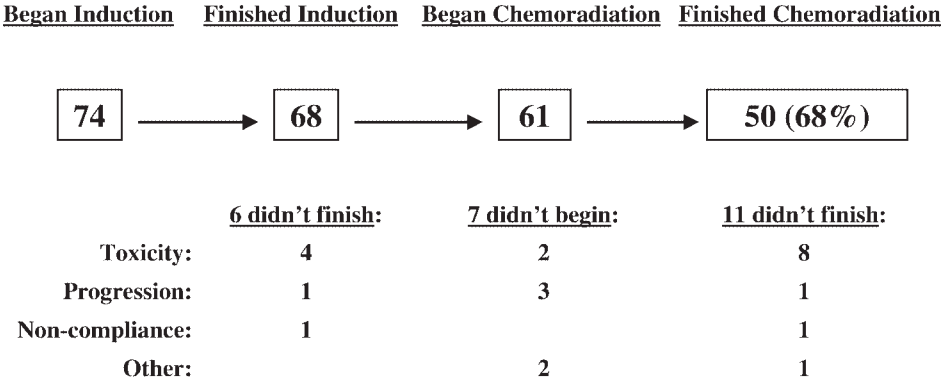


FIGURE 2. S0216: patient accounting.

Table 3. Toxicity grade ≥3.

Toxicity	No. (%)
Induction chemotherapy ($n = 74$)	
Nausea, vomiting	19 (26)
Anorexia	8 (11)
Dehydration	11 (15)
Renal dysfunction	1 (1)
Mucositis	15 (20)
Neutropenia	44 (59)
With fever	13 (18)
Thrombocytopenia	5 (7)
Anemia	3 (4)
Toxic death during induction	2 (3)
Total with ≥grade 3 toxicity	63 (85)
Concurrent chemoradiotherapy ($N = 58$)	
Nausea, vomiting	14 (24)
Anorexia	10 (17)
Dehydration	13 (22)
Renal dysfunction	5 (9)
Mucositis	28 (48)
Neutropenia	18 (31)
With fever	3 (5)
Thrombocytopenia	4 (7)
Anemia	5 (9)
Toxic death during chemoradiotherapy	2 (3)
Total with ≥grade 3 toxicity	53 (91)

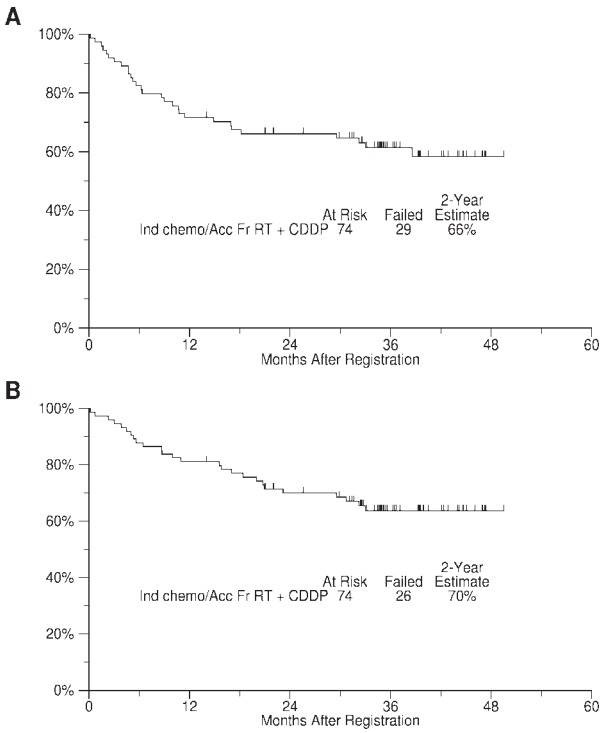


FIGURE 3. Progression-free (**A**) and overall (**B**) survival.

concurrent chemoradiotherapy in the 58 patients for whom data are available. Grade 3-4 mucositis was experienced by 48% of patients and grade 3-4 neutropenia by 31%. Hospitalization for neutropenic fever was required in 5% of patients. There were 2 additional toxic deaths during concurrent chemoradiotherapy, 1 from febrile neutropenia and 1 from a cardiac cause. Overall, 91% of patients experienced at least 1 grade 3 or greater toxicity during concurrent chemoradiotherapy.

After induction therapy, an unconfirmed clinically complete response was identified at the primary site in 12 patients (16%), and in the neck in 8 of the 65 patients (12%) with lymph node involvement at baseline. An overall complete response was documented in 5 patients (7%). After concurrent chemoradiotherapy, a primary site complete response was noted in 25 (34%) patients, a complete response in the neck was noted in 20 of 65 patients (31%) with nodal involvement at baseline, and an overall complete response was documented in 21 patients (28%).

With a median follow-up of 36 months (range, 14–50), the 2-year and 3-year progression-free survival estimates were 66% (95% CI: 55%–77%) and 61% (95% CI: 50%–73%), respectively (Figure 3A). The 2-year and 3-year overall survival estimates were 70% (95% CI: 60%–81%) and 64% (95% CI: 52%–75%), respectively (Figure 3B).

The analysis of patterns of failure is displayed in Table 4, but is not terribly revealing. Disease progression or death occurred in 29 patients, 12 of whom died before disease progression could be documented. Second, primary malignancies were identified in 4 patients: 2 with lung cancer, and 1 each with kidney and colon cancer. All 4 patients were alive, without evidence of their head and neck cancer, at the time of this analysis.

Table 4. Patterns of treatment failure.

	No. of patients
Disease progression	17
Local failure	3
Regional failure	5
Local and regional failure	5
Distant metastases	4
Death without disease progression	12
Toxicity	4
Cardiac disease	2
Infection (unrelated)	2
Lung disease	1
Unknown (disease-free)	3

DISCUSSION

In this cohort of patients with locoregionally advanced squamous cell head and neck cancer, this aggressive sequential treatment schedule produced very encouraging 2-year progression-free and overall survival rates. It should be pointed out that a significant fraction of these patients were from community-based oncology affiliates of larger Southwest Oncology Group member institutions, suggesting that this kind of intensive treatment can be successfully administered in the community.

At first glance, the overall complete response rates of only 7% after 3-drug induction chemotherapy and 28% after concurrent chemoradiotherapy seem disappointingly low, particularly in a patient population being treated with curative intent. These results must be viewed with caution, however, given the constraints of the RECIST definition of a complete response. Furthermore, residual radiographic abnormalities of measurable lesions are frequently found after chemotherapy and radiation and often do not reflect residual cancer. Many of the patients who did not achieve a formal complete response remain alive and progression free, years after completing treatment. In patients with this disease, the progression-free and overall survivals are far better measures of treatment effect than the complete response rate.

It must be stressed, however, that this is a very toxic treatment regimen. More than 90% of patients experienced at least 1 grade 3 or greater toxicity, and many patients experienced multiple toxicities. Four of the 74 patients (5%) in this trial died from treatment-related complications. Although this toxicity is in keeping with that observed in other similar multimodality treatment trials, it clearly strains the limitations of acceptability for any clinical treatment program. This toxicity and the potential for toxic death underscore how important it is that both treating physician and institution are familiar with this approach to head and neck cancer, and with the necessary supportive care.

The treatment could be completed and therefore proved feasible in 68% of patients in this study. It is important, however, to examine this notion of feasibility within the context of other recent trials in this disease, particularly those conducted in a cooperative group setting. Feasibility has been reported from similar cooperative group studies of chemotherapy and radiation for squamous cell head and neck cancer. In studies using radiation and single-agent cisplatin, even when that radiation is administered using an altered fractionation schedule, the feasibility has, in general, ranged from 83% to 85%.[2,4,25] When treatment becomes more complex, however, utilizing adjuvant chemotherapy,[3] concurrent multiagent chemotherapy,[2] or sequential treatment regimens similar to this trial,[20] the feasibility drops to between 55% and 73%, results more in keeping with this study. Clearly, there is a trade-off between the aggressiveness and complexity of a treatment regimen and the likelihood that it can be completed. The obvious concern is that these more aggressive and more complex treatment regimens may ultimately not improve outcome if the treatment cannot be completed.

It should be noted that 30% of the patients in this trial had stage III tumors. These patients may have been successfully treated with less intensive or less complicated regimens. It is of critical importance that we continue to attempt to identify selection factors that might better suggest which patients require the most aggressive therapies and which patients should be treated less intensively, or, alternatively, with surgery. The University of Michigan group has, for example, suggested that in laryngeal cancer, failure to respond to a single course of induction chemotherapy may identify a patient less likely to do well with chemoradiotherapy who might be better treated surgically.[26]

This phase II trial reports the feasibility and toxicity of this kind of sequential treatment approach and suggests that there is considerable efficacy in this patient population. This kind of sequential treatment schedule, however, remains investigational. Although theoretically attractive, the value of induction chemotherapy prior to definitive concurrent chemoradiotherapy has not been firmly established. We await the results of the phase III randomized trials currently being conducted that address this question.[13]

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