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Effect of Standard Radiotherapy With Cisplatin vs Accelerated Radiotherapy With Panitumumab in Locoregionally Advanced Squamous Cell Head and Neck Carcinoma
A Randomized Clinical Trial

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IMPORTANCE The Canadian Cancer Trials Group study HN.6 is the largest randomized clinical trial to date comparing the concurrent administration of anti–epidermal growth factor receptor (EGFR) monoclonal antibodies with radiotherapy (RT) to standard chemoradiotherapy in locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).

OBJECTIVE To compare progression-free survival (PFS) in patients with LA-SCCHN treated with standard-fractionation RT plus high-dose cisplatin vs accelerated-fractionation RT plus the anti-EGFR antibody panitumumab.

DESIGN, SETTING, AND PARTICIPANTS A randomized phase 3 clinical trial in 17 Canadian centers. A total of 320 patients were randomized between December 2008 and November 2011.

INTERVENTIONS Patients with TanyN+M0 or T3-4N0M0 LA-SCCHN were randomized 1:1 to receive standard-fractionation RT (70 Gy/35 over 7 weeks) plus cisplatin at 100 mg/m² intravenous for 3 doses (arm A) vs accelerated-fractionation RT (70 Gy/35 over 6 weeks) plus panitumumab at 9 mg/kg intravenous for 3 doses (arm B).

MAIN OUTCOMES AND MEASURES Primary end point was PFS. Due to an observed declining event rate, the protocol was amended to a time-based analysis. Secondary end points included overall survival, local and regional PFS, distant metastasis-free survival, quality of life, adverse events, and safety.

RESULTS Of 320 patients randomized (268 [84%] male; median age, 56 years), 156 received arm A and 159 arm B. A total of 93 PFS events occurred. By intention-to-treat, 2-year PFS was 73% (95% CI, 65%-79%) in arm A and 76% (95% CI, 68%-82%) in arm B (hazard ratio [HR], 0.95; 95% CI, 0.60-1.50; P = .83). The upper bound of the HR 95% CI exceeded the prespecified noninferiority margin. Two-year overall survival was 85% (95% CI, 78%-90%) in arm A and 88% (95% CI, 82%-92%) in arm B (HR, 0.89; 95% CI, 0.54-1.48; P = .66). Incidence of any grade 3 to 5 nonhematologic adverse event was 88% in arm A and 92% in arm B (P = .25).

CONCLUSIONS AND RELEVANCE With a median follow-up of 46 months, the PFS of panitumumab plus accelerated-fractionation RT was not superior to cisplatin plus standard-fractionation RT in LA-SCCHN and noninferiority was not proven. Despite having negative results, HN.6 has contributed important data regarding disease control and toxic effects of these treatment strategies.
Treatment strategies for patients with locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) have continued to evolve over the past decade, with the ultimate goal of developing new approaches that can enhance the therapeutic index over existing regimens. Based on the results of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), 1 cisplatin-based chemotherapy administered concurrently with radiation therapy (RT) remains the standard of care in LA-SCCHN. High-dose cisplatin administered at 100 mg/m² represents the standard systemic agent in the control arm of randomized clinical trials that have recently been reported or completed accrual. 2-3 In the Radiation Therapy Oncology Group (RTOG) 0129 trial, 4 there was no statistically significant difference in efficacy outcomes and in acute or late toxic effects between 3 cycles of high-dose cisplatin given with standard-fractionation RT (SFX) vs 2 cycles of high-dose cisplatin given with accelerated-fractionation RT (AFX). These results justify the choice of cisplatin plus SFX as a control arm in phase 3 trials of LA-SCCHN testing new treatment strategies, including in the present HN.6 study.

The concomitant administration of the anti–epidermal growth factor receptor (EGFR) inhibitor monoclonal antibody cetuximab with RT led to improved survival compared with RT alone in LA-SCCHN. High-dose cisplatin administered at 100 mg/m² represents the standard systemic agent in the control arm of randomized clinical trials that have recently been reported or completed accrual. 2-3 In the Radiation Therapy Oncology Group (RTOG) 0129 trial, 4 there was no statistically significant difference in efficacy outcomes and in acute or late toxic effects between 3 cycles of high-dose cisplatin given with standard-fractionation RT (SFX) vs 2 cycles of high-dose cisplatin given with accelerated-fractionation RT (AFX). These results justify the choice of cisplatin plus SFX as a control arm in phase 3 trials of LA-SCCHN testing new treatment strategies, including in the present HN.6 study.

The concomitant administration of the anti–epidermal growth factor receptor (EGFR) inhibitor monoclonal antibody cetuximab with RT led to improved survival compared with RT alone in LA-SCCHN in the IMCL-9815 study. 4 In subgroup analysis, the application of AFX (concomitant boost) demonstrated greater benefit from the addition of cetuximab over SFX, with a hazard ratio (HR) of 0.64. 4 With this observation, HN.6 was designed as a randomized, controlled phase 3 clinical trial with the primary objective of comparing the efficacy end point of progression-free survival (PFS) in patients with LA-SCCHN treated with SFX plus high-dose cisplatin vs AFX plus the anti-EGFR antibody panitumumab.

Methods

Study Design and Patients

HN.6 is a multicenter, open-label, randomized controlled phase 3 study designed by a protocol committee that included members of Canadian Cancer Trials Group (study protocol in Supplement 1). The institutional review boards of all participating institutions approved the protocol, and all participants gave written informed consent.

Selected eligibility criteria included histologically or cytopologically confirmed, locoregionally advanced squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx defined as T(any), N+, M0 or T3-4, NO, M0. Other key eligibility criteria included age 18 years or older; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; and adequate bone marrow, liver, and kidney functions. A complete list of all eligibility criteria in the study protocol is provided as eText in Supplement 2.

Randomization

Eligible patients were stratified according to T category (T1-3 vs T4), nodal status (N0-1 vs N2 vs N3), RT delivery modality (intensity-modulated RT vs 3-dimensional conformal RT), and anatomic location (hypopharynx vs oral cavity vs oropharynx vs larynx). Patients were randomly assigned between December 30, 2008, and November 7, 2011, at a 1:1 ratio to the control regimen of SFX and cisplatin 100 (arm A) or to the investigational regimen of AFX and panitumumab (arm B). Randomization was performed by the Canadian Cancer Trials Group Statistics and Operations Office with the use of a minimization procedure that included stratification factors and treatment center. 5

Procedures

Radiation Therapy

All patients received RT with either concomitant cisplatin (arm A) or panitumumab (arm B). In arm A, RT was delivered once daily to a total dose of 70 Gy in 35 fractions over 7 weeks, and in arm B, the same total dose was delivered in 35 fractions over 6 weeks by introducing a twice-daily treatment once per week for 5 weeks. Regions at risk of harboring microscopic disease were treated to 56 Gy in 35 fractions. Additional RT details are provided as eText in Supplement 2.

Systemic Therapy

For patients randomly assigned to arm A, cisplatin was administered intravenously at a dose of 100 mg/m² on days 1, 22, and 43 of RT. Premedication and hydration were given in accordance with institutional standard. For patients randomly assigned to arm B, panitumumab was administered intravenously at a dose of 9 mg/kg over 60 to 90 minutes (plus or minus 15 minutes) every 3 weeks, starting 1 week prior to RT start, on days –7, 15, and 36 of RT. All adverse events were graded using the NCI Common Terminology Criteria for Adverse Events, version 3.0.

Dose modification and response evaluation details are provided in eText in Supplement 2.

Statistical Analysis

The primary end point of this study was PFS, defined as the time from randomization until the first objective observation of disease progression or death from any cause. Progression was defined by first event of the following: locoregional progression or recurrence; distant metastasis;
A total of 320 patients were randomized between December 2008 and November 2011, with 160 assigned to arm A and 160 assigned to arm B. Among them, 4 patients in arm A and 1 patient in arm B either did not receive systemic therapy or withdrew their consents before the first dose of treatment. Therefore, a total of 315 patients (156 on arm A and 159 on arm B) were included in the treatment status and safety analyses (Figure 1). Patients in both arms had similar baseline characteristics (Table I). The median follow-up was 46 months (range, 0.1-64.3 months).

**Efficacy**
A total of 93 PFS events occurred at the time of the clinical data cutoff, 50 on arm A and 43 on arm B, with details about the type of first event listed in eTable 1 in Supplement 2. The Kaplan-Meier curve for the primary end point of PFS by treatment arms is depicted in Figure 2. There was no statistically significant difference between the 2 treatment arms (HR, 0.95; 95% CI, 0.60-1.50 [arm B vs arm A], stratified log rank test P = .83). The 2-year PFS for arm A was 73% (95% CI, 65%-79%) and 76% for arm B (95% CI, 68%-82%). Because the upper bound of the HR 95% CI is 1.50, which exceeds the prespecified noninferiority margin of 1.15, the trial does not meet the noninferiority criterion in the comparison of arm B to arm A in the PFS end point. By multivariable analysis, anatomic location (oropharynx vs larynx; P = .001), ECOG performance status (P = .02), p16 status (P = .006), and T category (P < .001) were significant predictors of PFS.

A subgroup analysis based on planned subgroups (ECOG performance status, T category, N status, primary site) and unplanned subgroups (p16 status and smoking history) is shown in eFigure in Supplement 2. No statistically significant differences in the relative effect of panitumumab plus AFX compared with cisplatin plus SFX on PFS were seen across any of the subgroups.

Among the 320 patients accrued to this trial, a total of 75 had died at the time of clinical data cutoff, 43 on arm A and 32 on arm B. The causes of death with details are summarized in eTable 2 in Supplement 2. The Kaplan-Meier curve for the secondary end point of OS by treatment arms is depicted in Figure 3. There was no statistically significant difference between the 2 treatment arms (HR, 0.89; 95% CI, 0.54-1.48 [arm B vs arm A], stratified log rank test P = .66). The 2-year OS for arm A was 85% (95% CI, 78%-90%) and 88% for arm B (95% CI, 82%-92%).

There were no statistically significant differences in any of the other secondary efficacy end points: 2-year cumulative incidence of local recurrence for arm A was 4.5% (95% CI, 1.2%-7.8%) and arm B was 7.0% (95% CI, 3.0%-10.9%), the cause-specific HR, 2.00 (95% CI, 0.68-5.90 [arm B vs arm A]; P = .20); 2-year cumulative incidence of regional recurrence for arm A was 2.5% (95% CI, 0.1%-5.0%) and arm B was 3.8% (95% CI, 0.8%-6.8%), the cause-specific HR, 1.46 (95% CI, 0.30-4.97 [arm B vs arm A]; P = .64); and 2-year cumulative incidence of distant recurrence for arm A was 10.2% (95% CI, 5.5%-
15.0%) and arm B was 10.1% (95% CI, 5.4%-14.9%), the cause-specific HR, 1.01 (95% CI, 0.49-2.11 [arm B vs arm A]; \( P = .97 \)).

Safety

Grade 3 or higher adverse events of interest of any attribution are summarized in Table 2. All-grade on-treatment adverse events of any attribution are provided in eTable 3 in Supplement 2. In general, arm A study treatment led to increased otoxic effects such as hearing loss and tinnitus, gastrointestinal toxic effects such as nausea, vomiting, and dehydration, renal toxic effects, and weight loss. Arm B study treatment resulted in a greater incidence of skin toxic effects and grade 3 or higher mucositis. High-grade hematologic and biochemical adverse events were uncommon in both study arms, with slightly increased frequencies observed in bone marrow toxic effects and electrolyte disturbances such as hypokalemia, hypomagnesemia, and hyponatremia in arm A compared with arm B. At 6 months after completion of study treatment, 9 of 143 patients who had functional oral intake status available were feeding tube dependent for feeding in arm A (6%) and 19 of 147 patients (13%) were tube dependent in arm B. At 12 months after completion of study treatment, feeding tube dependency rates were 3% and 8%, respectively, for arms A and B. There were 3 treatment-related deaths on study (eTable 2 in Supplement 2).

Treatment Delivery

Systemic treatment dose intensities and RT delivery data are provided in eTable 4 in Supplement 2. Only 99 of 156 (63%) patients in arm A received all 3 cycles of cisplatin whereas 144 of 159 (91%) patients in arm B received all 3 cycles of panitumumab. The mean (SD) cumulative dose was 245.8 (56.4) mg/m² (range, 92.4-306.6 mg/m²) of cisplatin in arm A and 26.5 (2.99) mg/kg (range, 16.3-32.8 mg/kg) of panitu-

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td></td>
<td>Arm A: Cisplatin + SFX (( n = 160 ))</td>
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<td>Sex, No. (%)</td>
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<tr>
<td>Female</td>
<td>26 (16)</td>
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<tr>
<td>Male</td>
<td>134 (84)</td>
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<td>Age, Median, y</td>
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<td>≥60 y, No. (%)</td>
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<td>RT delivery modality, No. (%)</td>
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<td>IMRT</td>
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</tr>
<tr>
<td>3D CRT</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

Abbreviations: AFX, accelerated-fractionation radiation therapy; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; IHC, immunohistochemistry; IMRT, intensity-modulated radiation therapy; RT, radiation therapy; SFX, standard-fractionation radiation therapy; 3D CRT, 3-dimensional conformal radiation therapy.
mumab in arm B, suggesting that overall systemic treatment dose intensity was greater in arm B than arm A. Adherence to RT delivery was high, with completion of 70 Gy in 98% of patients in both arms, with mean RT duration of 49 (range, 43-64) days in arm A and 42 (range, 32-51) days in arm B. Radiotherapy interruptions due to toxic effects were observed in 2 (1.3%) and 3 (1.9%) in arms A and B, respectively. At final retrospective external review by Quality Assurance Review Center, treatment adherence was deemed appropriate in 150 (96%) and 157 (99%) of plans in arms A and B, respectively.

Quality of Life
Detailed quality-of-life analyses are reported in a separate publication. There was no statistically significant difference between the 2 study arms in the primary quality-of-life end point in this study, defined as the median change of 6 points or more in the overall score from baseline to 1 year on the Functional Assessment of Cancer Therapy–Head and Neck questionnaire (arm A = −1.70, arm B = −4.81; P = .19).

Discussion
In this randomized controlled phase 3 trial, superiority or noninferiority in PFS of panitumumab plus AFX compared with cisplatin plus SFX in LA-SCCHN was not demonstrated. There were also no statistically significant differences between the 2 treatment arms with respect to secondary end points. There are several potential reasons to explain these outcomes.

First, 2 randomized phase 2 trials investigating panitumumab and RT in combination using either a chemo-additive approach (CONCERT-1) or a chemo-sparing approach (CONCERT-2) in LA-SCCHN have recently been published, both reporting negative results in their primary end point of 2-year locoregional control. These results are aligned with the findings of HN.6 and may be attributable to the use of panitumumab (a fully human immunoglobulin G2 antibody) instead of other anti-EGFR monoclonal antibodies, such as cetuximab (a chimeric immunoglobulin G1 antibody).
antibody) that can elicit antibody-dependent cell-mediated cytotoxicity as a mechanism of antitumor activity. Currently, cetuximab is the only anti-EGFR antibody approved by the US Food and Drug Administration for the treatment of LA-SCCHN in combination with RT. Furthermore, cetuximab demonstrated an improvement in OS when combined with platinum and fluorouracil (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer [EXTREME] trial) in the recurrent or metastatic SCCHN setting, whereas panitumumab given with the same chemotherapy doublet (Study of Panitumumab Efficacy in Patients with Recurrent and/or Metastatic Head and Neck Cancer [SPECTRUM] trial) did not achieve a statistically significant OS benefit compared with chemotherapy alone. While the difference between the EXTREME and SPECTRUM trials may not be solely due to the anti-EGFR antibody under evaluation, as variations in the study populations and trial designs exist, it is unlikely that a well-powered, direct head-to-head comparison of these 2 agents will ever be performed, in contrast to the case of advanced colorectal cancer, in which more than 1000 patients were enrolled to confirm noninferiority.

Second, HN6 was designed in the era when evidence for the biological significance of HPV status in SCCHN was just emerging. As such, it did not specifically include or exclude participants based on their tumoral HPV or p16 status, unlike RTOG 1016 (NCT01302834) or the Trans-Tasman Radiation Oncology Group (TROG) study 12.01 (NCT01855451), which are both phase 3 trials comparing chemoradiotherapy vs bioradiotherapy in HPV-related oropharyngeal cancer. RTOG 1016 compared AFX plus cisplatin against AFX plus cetuximab with an OS end point, whereas TROG 12.01 compared SFX plus panitumumab against SFX with weekly cisplatin, with a primary end point of symptom severity from baseline to week 20 after treatment. If the addition of anti-EGFR monoclonal antibody to RT portends a differential effect in LA-SCCHN based on HPV status, then the unselected patient population of HN.6 may have diluted such an effect. Although subgroup analysis by p16 status was not significant in HN.6, there are known limitations with small-subset evaluations. Retrospective analysis of the IMCL-9815 study showed that the addition of cetuximab to RT benefited patients with locoregionally advanced oropharyngeal cancer regardless of p16 status, although the magnitude of the gain seemed to be more pronounced among patients with p16-positive tumors. It is also notable that there were differences in the patient populations of CONCERT-1, CONCERT-2, and HN.6 that might render their direct comparisons incongruous. In the CONCERT trials, patients with oropharyngeal cancer made up approximately 48% to 53% of the study populations, while this anatomical subgroup accounted for 81% in HN.6. Among patients with oropharyngeal cancer, the proportions of p16-positive tumors were 28%, 16%, and 68% in CONCERT-1, CONCERT-2, and HN.6, respectively. Given the nearly identical 2-year PFS between the 2 arms in HN.6 (73% vs 76%; HR, 0.95; 95% CI, 0.60-1.50; \( P = .83 \)), in contrast to the higher 2-year PFS in the chemoradiotherapy arm compared to bioradiotherapy arm in CONCERT-2 (62% vs 41%; HR, 1.73; 95% CI, 1.07-2.81; \( P = .03 \)), it is possible that bioradiotherapy may be a suitable alternative to chemoradiotherapy in p16-positive oropharyngeal cancers, a question that will be more definitively addressed as the results of RTOG 1016 become available.

Last, due to the low event rate, HN.6 lacked the power to detect the differences in PFS outcome as originally designed both for superiority and noninferiority. RTOG 1016 has a sample size nearly 3 times that of HN.6, but is designed as a classic non-inferiority study with a 7.6%-point lower boundary for OS at 5 years for the inferior margin of the cetuximab arm. It is plausible that a small difference exists in efficacy between the 2 treatment arms in HN.6 but was not detected due to the limited sample size.

The design of HN.6 involved an experimental arm that differed from the control arm with respect to the RT and systemic therapy components, making it difficult to assess the relative contribution of each variable had the trial outcome been positive. However, the intention was to combine EGFR inhibition (panitumumab) with the most optimal RT fractionation scheme using AFX as previously reported, and to assess the relative efficacy of 2 different combination therapies, similar to the approach in RTOG 0129.
Conclusions

Despite the inability to demonstrate superiority or noninferiority of bioradiotherapy over chemoradiotherapy, HN.6 has contributed important outcome data associated with these treatment strategies. It offered a valuable opportunity to standardize intensity-modulated RT and ensure quality of RT techniques across its participating sites. It also provided a platform for detailed assessment of quality of life, swallowing symptoms, and physiologic swallowing function among patients with LA-SCCHN receiving concurrent combined therapy, which will be an invaluable source of data to characterize the impact of disease and treatment from the patient perspective. A clinically well-annotated repository of tumor and blood-based biospecimens has been collected as part of the correlative science objective of this study, which will be germane to hypotheses-generated translational research to better elucidate the role of EGFR inhibition in this disease.

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Author Contributions: Drs Chen and Parulekar had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Siu, Waldron, Chen, Winquist, Wright, Hay, Ringash, Johnson, Breen, FitzGerald, O’Sullivan, Parulekar.
Acquisition, analysis, or interpretation of data: Siu, Waldron, Chen, Winquist, Nabil, Hay, Ringash, Liu, Shenouda, Chason, Pearce, Butler, Chen, FitzGerald, Childs, Montenego, Parulekar.
Drafting of the manuscript: Siu, Waldron, Chan, Wright, Chason, FitzGerald, Parulekar.
Critical revision of the manuscript for important intellectual content: Siu, Waldron, Chen, Winquist, Nabil, Hay, Ringash, Liu, Johnson, Shenouda, Chason, Pearce, Butler, Breen, Chen, FitzGerald, Montenego, Parulekar.
Statistical analysis: Chen, Liu, O’Sullivan.
Administrative, technical, or material support: Siu, Wright, Liu, Johnson, Shenouda, Pearce, Breen, Chen, FitzGerald, Montenego, Parulekar.
Study supervision: Siu, Waldron, Chen, Winquist, Chason, FitzGerald, Montenego, Parulekar.

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