CONCERT-1, an additional piece in the puzzle of (bio)-(chemo)-radiation

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CONCERT-1 (1) is an international, open-label, randomized, controlled, phase 2 trial, in which 150 patients with previously untreated stage III, IVa, or IVb, locally advanced (LA) non-nasopharyngeal squamous cell carcinoma of the head and neck (HNSCC) from 41 sites in 9 countries were randomly assigned 2:3 to open-label concurrent chemoradiotherapy (CCRT) (three cycles of cisplatin 100 mg/m^2) or panitumumab plus CCRT (three cycles of intravenous panitumumab 9.0 mg/kg every 3 weeks plus cisplatin 75 mg/m^2). All patients received 70 Gy to gross tumor and 50 Gy to areas at risk for subclinical disease with standard fractionation. The primary endpoint was local-regional control at 2 years, which was 68% (95% CI, 54–78%) in the CCRT group and 61% (95% CI, 50–71%) in the panitumumab plus CCRT group. The most frequent grade 3/4 adverse events were dysphagia (27% with CCRT *vs.* 40% with CCRT plus panitumumab), mucositis (24% *vs.* 55%) and radiodermatitis (13% *vs.* 31%). Serious adverse events were also more common in the CCRT plus panitumumab group (32% with CCRT *vs.* 43% in the CCRT plus panitumumab group). Median radiation therapy relative dose intensity in patients receiving CCRT was 69%, representing a median of 70 Gy (IQR 70–70) over a median of 51 days (IQR 49–53), and 66% [representing a median of 70 Gy (IQR 70–70) over a median of 52 days (IQR 50–57)] for patients receiving panitumumab plus CCRT. Major radiation therapy deviations occurred in 8% of the patients receiving CCRT and in 14% of the patients receiving CCRT plus panitumumab. Treatment interruptions greater than ten cumulative days occurred in 3% and 16% of the patients, respectively. Although this was a phase 2 trial with a sample size that was not powered to do any formal hypothesis testing, the results nevertheless strongly suggested that the addition of panitumumab to CCRT conferred no benefit and moreover was associated with more in-field radiation toxicity leading to more long treatment interruptions, which is known to have a negative impact on efficacy. In fact, in both arms, the median treatment time (51 and 52 days, respectively) was longer than the optimal treatment time of 49 days (7×7 days). By design, the planned cisplatin dose in the CCRT plus panitumumab arm was 25% lower than in the CCRT alone arm, which may also have contributed to the lower loco-regional control rate (1). Cumulative cisplatin dose is known to be associated with a better outcome (2,3).

Panitumumab is an IgG2 monoclonal antibody. Zalutumumab and cetuximab are EGFR-directed monoclonal antibodies of the IgG1 isotype. Panitumumab is as effective as zalutumumab in recruiting ADCC by myeloid effect cells in contrast to natural killer (NK) cell-mediated ADCC, which is only induced by the IgG1 monoclonal antibodies. Despite these additional potentially beneficial activities, cetuximab and zalutumumab also failed to improve the outcome when added to chemoradiation (4). Cetuximab in association with CCRT was studied in RTOG 0522 (5) in which 891 patients with untreated, stage III or IV (T2N2-3M0 or T3–4, any N, M0) non-nasopharyngeal LA-HNSCC were randomly assigned 1:1 to radiotherapy with concurrent cisplatin without (arm A) or with cetuximab (arm B). Radiotherapy consisted of accelerated radiotherapy (AFX) (72 Gy in 42 fractions given over 6 weeks, using twice-a-day irradiation for 12 treatments). When IMRT was used, a different

accelerated schedule of twice-a-day dosing once a week for 5 weeks delivered 70 Gy in 35 fractions (2 Gy per fraction) over 6 weeks per the Danish Head and Neck Cancer Group (DAHANCA) 6 and 7 studies. Cisplatin dose was 100 mg/m^2 on days 1 and 22 in both arms (5). The cetuximab dose in arm B was 400 mg/m^2 1 week before CCRT followed by weekly 250 mg/m^2 during CCRT. After a median follow up of 3.8 years, no significant differences were found between arms in progression-free survival (PFS) (primary end point), overall survival (OS), locoregional failure (LRF) or distant metastasis (DM). The 3-year PFS probabilities were 61.2% (95% CI, 56.7–65.8%) for arm A and 58.9% (95% CI, 54.2–63.6%) for arm B (P=0.76). The 3-year probabilities for OS were 72.9% (95% CI, 68.7–77.1%) for arm A and 75.8% (95% CI, 71.7–79.9%) for arm B (P=0.32); the 3-year LRF probabilities were 19.9% (95% CI, 16.2–23.7%) for arm A and 25.9% (95% CI, 21.7–30.1%) for arm B (P=0.97); and the 3-year DM probabilities were 13.0% (95% CI, 9.9–16.2%) for arm A and 9.7% (95% CI, 6.9–12.6%) for arm B (P=0.08). The addition of cetuximab led to more frequent treatment interruptions and more grade 3/4 mucositis (43.2% *vs.* 33.3%, respectively), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity (5).

In contrast, while the association of an EGFR-directed monoclonal antibody to CCRT does not improve the outcome and increases the toxicity, the addition of chemotherapy to radiotherapy plus cetuximab is associated with an improved PFS and LCR as demonstrated in the GORTEC 2007-01 trial (6) in which 406 patients with non-nasopharyngeal non-metastatic stage III/IV HNSCC with no or limited nodal spread (N0–N2a) were randomized 1:1 between radiotherapy (70 Gy, 2 Gy/day, 5 days/week) plus cetuximab (arm A) and radiotherapy plus cetuximab plus concurrent chemotherapy (three cycles of carboplatin 70 mg/m^2/d + 5FU 600 mg/m^2/d d1–4). After a median follow up of 4.4 years, 3-year PFS rate (primary endpoint) was 52.3% in arm B *vs.* 40.5% in arm A [hazard ratio (HR) =0.73; 95% CI, 0.57–0.94; P=0.015]. For loco-regional control, the HR was 0.54 (95% CI, 0.38–0.76; P=0.0005) in favor of arm B. The OS was not significantly different between both arms (HR =0.80; 95% CI, 0.61–1.05; P=0.11). Mucositis and leucopenia were significantly more frequent in arm B (6). In DAHANCA 19 (7), 619 patients were randomized to receive radiotherapy 68 Gy, 2 Gy/fraction, 6 fractions/week, and concomitant daily nimorazole, and in case of stage III or IV tumors, weekly cisplatin 40 mg/m^2 either with or without zalutumumab. The 4-year locoregional control rate (primary endpoint) was 71% in the zalutumumab arm versus 73% in the control arm (HR =1.16; 95% CI, 0.83–1.61). There was no benefit of adding zalutumumab to CCRT or to radiotherapy alone. Similarly, the EGFR-directed tyrosine kinase inhibitors gefitinib and erlotinib also failed to improve the outcome when added to CCRT (8,9). Two randomized phase II trials and a meta-analysis (10) strongly suggested that the combination of radiotherapy with an anti-EGFR antibody is inferior to CCRT (11,12). After 3 cycles of TPF induction chemotherapy, radiotherapy with cetuximab is associated with more grade 3/4 mucositis (44.6% *vs.* 31.7%), dermatitis (21.8% *vs.* 2%) skin toxicity (6.9% *vs.* 0%) as compared to CCRT (13).

Accelerated fractionation radiotherapy with panitumumab is not superior to standard CCRT (14). In the NCIC Clinical Trials Group HN.6 trial 320 patients with Tany N+ M0 or T3/4N0M0 LA-HNSCC (81% oropharynx of whom 81% were p16+) were randomized 1:1 to receive standard fractionation radiotherapy (70 Gy/35 over 7 weeks) plus cisplatin at 100 mg/m^2 for 3 doses on weeks 1, 4 and 7 (arm A) or AFX (70 Gy/35 over 6 weeks) plus panitumumab at 9 mg/kg IV for 3 doses on weeks 1, 3 and 6 (arm B). After a median follow-up of 46.4 months 2-year PFS (primary endpoint) was 73% (95% CI, 65–79%) in arm A and 76% (95% CI, 68–82%) in arm B (HR =0.95; 95% CI, 0.6–1.5; P=0.83). Upper bound of HR's 95% CI exceeded the pre-specified non-inferiority margin. Two-year OS 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=0.66). The incidence of any ≥ grade 3 non-hematologic adverse events was 88% in arm A and 91% in arm B (P=0.25) (14).

In conclusion, Mesia *et al.* have added one more piece of the puzzle on the role of anti-EGFR antibodies in LA-HNSCC, which is now quasi complete.

CCRT is superior to radiotherapy plus anti-EGFR, CCRT plus anti-EGFR is superior to radiotherapy plus anti-EGFR, CCRT plus anti-EGFR is not superior to CCRT alone, AFX plus anti-EGFR is not superior to conventionally fractionated radiotherapy plus cisplatin and non-inferiority has not been demonstrated.

The conclusion from these equations is that conventionally fractionated RT in combination with high-dose cisplatin three times during RT still is the standard of care in patients with LA-HNSCC. Some patients cannot tolerate cisplatin-based CCRT. It is unclear whether radiotherapy plus an anti-EGFR directed monoclonal antibody is equivalent to a carboplatin/5-FU-based regimen in this patient population although the combined data

suggest that the latter is probably to be preferred.

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Footnote

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Comment on: Mesía R, Henke M, Fortin A, *et al.* Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial. Lancet Oncol 2015;16:208-20.

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