HEAD AND NECK CANCER

COMBINATION THERAPY: CHEMOTHERAPY + RADIATION THERAPY

CETUXIMAB – RADIATION

Cetuximab	400 mg/m^2	IV	One dose on week 1
Cetuximab	250 mg/m^2	IV	Once a week of weeks 2 – 8

Followed by

Radiation*	Various radiation schemas were used including: Once daily radiation for a total of 35 fractions – each of 2 Gy to a total dose of 70 Gy delivered over 7 weeks; Twice daily radiation schedule that included 60 – 64 fractions to a total dose of 72 – 76.8 Gy delivered over 6 – 6.5 weeks. A concomitant boost was also permitted administered in 42 fractions to a total dose of 72 Gy delivered over 6 weeks

*Radiation to begin in week 2.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m^2 IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

Reference: Bonner JA, et al. *N Engl J Med* 2006;354:567 – 78.

CISPLATIN – HYPERFRACTIONATED RADIATION

Cisplatin	20 mg/m^2/day	IV*	Days 1 – 5 (consecutive days) during week 1 and 5 or 6 of radiotherapy. Administer 1.5 hours before the afternoon radiotherapy session
Radiation	Hyperfractionated radiation of 1.2 Gy administered twice daily with an interfraction interval of 6 hours. Total radiation dose is 72 – 76.8 Gy		

*Routine pre- and post-hydration administered.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m^2 IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

Reference: Huguenin P, et al. *J Clin Oncol* 2004;22:4665 – 73.

CISPLATIN (WEEKLY) – HYPERFRACTIONATED RADIOTHERAPY

Cisplatin	40 mg/m^2	IV*	Days 1, 8, 15, 22, 29 and 36
Radiation	The primary tumor and bilateral draining lymphatics above the clavicle are to be treated with 5 fractions per week over 5.5 weeks (days 1 – 38) with a single fraction of 1.8 Gy (to a total dose of 50.4 Gy). Starting the 4th week of treatment, additional radiation therapy was administered as a concomitant boost (days 22 – 38). The boost volume covers the primary tumor and the involved neck nodes. The dose was 1.5 Gy/day up to 19.5 Gy, resulting in a total tumor dose of 69.9 Gy		

*Administer over 30 minutes with adequate pre- and post-hydration.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m^2 IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

Reference: Beckmann GK, et al. *Head Neck* 2005;27:36 – 43.

CISPLATIN – RADIATION

Cisplatin	100 mg/m^2	IV*	Days 1, 22 and 43 during radiation
Radiation	70 Gy given in single, daily 2 Gy fractions		

*Routine pre- and post-hydration required.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m^2 IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

Reference: Adelstein DJ, et al. *J Clin Oncol* 2003;21:92 – 8.

PACLITAXEL – CISPLATIN – RADIATION

Paclitaxel‡	30 mg/m^2	IV	Days 1, 8, 15, 22, 29, 36 and 43
Cisplatin	20 mg/m^2	IV*	Days 2, 9, 16, 23, 30, 37 and 44
Radiation	70 Gy in 35 daily 2 Gy fractions delivered on Monday – Friday (for 5 weeks)		

‡Routine premedication administered; *Routine pre- and post-hydration required.

NOTE: Chemotherapy to be given prior to radiation on appropriate days. Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m^2 IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

Reference: Garden AS, et al. *J Clin Oncol* 2004;22:2856 – 64.

PACLITAXEL – CISPLATIN – 5-FLUOROURACIL – RADIATION (PCF)

Paclitaxel‡	175 mg/m^2	IV*	Day 1
Cisplatin	100 mg/m^2	IV**	Day 2
5-Fluorouracil	500 mg/m^2/day	CIVI	Days 2 – 6

‡Routine premedication administered; *Administer over 3 hours; **Routine pre- and post-hydration required.

Repeat cycle every 3 weeks for 3 courses.

Followed by

Cisplatin	100 mg/m^2	IV*	Days 1, 22 and 43
Radiation	70 Gy total dose administered in 35 fractions of 2Gy over a 7-week period. Nodal areas not clinically involved by tumor received a total dose of 50 Gy.		

*Routine pre- and post-hydration required.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m^2 IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

Reference: Hitt R, et al. *J Clin Oncol* 2005;23:8636 – 45.

HEAD AND NECK CANCER
ADJUVANT THERAPY

CISPLATIN – RADIATION

Cisplatin	100 mg/m^2	IV*	Days 1, 22 and 43 during radiation therapy
Radiation therapy	2 Gy/day Monday – Friday for 5 – 5.5 weeks to a total of 50 – 54 Gy. Close or positive margins received a 12 Gy boost (total 66 Gy) in 33 fractions over a period of 6.5 weeks.		

*Routine pre- and post-hydration required.

NOTE: Amifostine has been shown to be effective in reducing radiation-induced xerostomia. The most effective dose is 200 mg/m^2 IV over 3 – 5 minutes, administered at least 15 – 30 minutes prior to radiation three times weekly [Reference: Jellema AP, et al. *Cancer* 2006;107:544 – 53].

Reference: Bernier J, et al. *N Engl J Med* 2004;350:1945 – 52.

HEAD AND NECK CANCER
SYSTEMIC CHEMOTHERAPY

CARBOPLATIN – 5-FLUOROURACIL

Carboplatin	300 mg/m^2	IV*	Day 1
5-Fluorouracil	1000 mg/m^2/day	CIVI**	Days 1 – 4

*Administer over 5 – 10 minutes; **Administer as a continuous 24-hour infusion.

Repeat cycle every 28 days.

Reference: Forastiere AA, et al. *J Clin Oncol* 1992;10:1245 – 51.

CETUXIMAB

Cetuximab	400 mg/m^2	IV*#	Day 1, week 1
Cetuximab‡	250 mg/m^2	IV**	Day 8 and then weekly thereafter

#A test dose of 20 mg was administered before the first dose of cetuximab; *Administer over 2 hours; **Administer over 1 hour.

Continue until disease progression or unacceptable toxicity.

Reference: Vermoken JB, et al. *J Clin Oncol* 2007;25:2171 – 7.

CETUXIMAB – CISPLATIN

Cetuximab‡	400 mg/m^2	IV*#	Day 1, week 1
Cetuximab‡	250 mg/m^2	IV**	Day 8 and then weekly thereafter
Cisplatin	75 – 100 mg/m^2	IV**	Day 1

‡Patients were premedicated with dexamethasone 20 mg and diphenhydramine 50 mg IV 30 minutes before the cetuximab infusion; #A test dose of 20 mg was administered before the first dose of cetuximab, followed by an observation period of 30 minutes for signs of severe infusion reactions; *Administer over 2 hours; **Administer over 1 hour.

DOSE MODIFICATIONS: [1]A delay of cetuximab therapy for 2 consecutive weeks was allowed for patients with grade 3 skin toxicity; [2]Cetuximab was interrupted for up to 2 weeks in case of grade 3 skin reactions. If a grade 3 skin reaction occurred for the 2nd or 3rd time in the same patients, cetuximab doses were reduced to 200 and 150 mg/m^2, respectively. Recurrence of a grade 3 skin reaction despite 2 dose reductions warranted discontinuation of cetuximab.

Repeat cycle every 21 days

References: [1]Herbst RS, et al. *J Clin Oncol* 2005;23:5578 – 87; [2]Baselga J, et al. *J Clin Oncol* 2005; 23:5568 – 77; Burtness B, et al. *J Clin Oncol* 2005;23:8646 – 54.

CISPLATIN – CAPECITABINE

Cisplatin	75 mg/m^2	IV*	Day 1
	Followed by		
Capecitabine	1000 mg/m^2 BID	PO	Days 1 – 14

*Administer over 30 minutes with adequate pre- and post-hydration.

NOTE: Capecitabine available as 150 and 500 mg tablets.

Repeat cycle every 21 days for a maximum of 6 cycles.

Reference: Hitt R, et al. *Br J Cancer* 2004;91:2005 – 11.

CISPLATIN – 5-FLUOROURACIL

Cisplatin	100 mg/m^2	IV*	Day 1
5-Fluorouracil	1000 mg/m^2/day	CIVI**	Days 1 – 4

*Administer over 15 – 30 minutes with adequate pre- and post-hydration; **Administer as continuous 24-hour infusion daily.

Repeat cycle every 21 days.

Reference: Forastiere AA, et al. *J Clin Oncol* 1992;10:1245 – 51.

DOCETAXEL – CARBOPLATIN

Docetaxel‡	65 mg/m^2	IV*	Day 1
	Followed immediately by		
Carboplatin	AUC 6	IV**	Day 1

‡Routine premedication administered; *Administer over 1 hour; **Administer over 30 minutes.

Repeat cycle every 21 days until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS: Docetaxel dose was reduced by 25% if ANC nadir was $< 1 \times 10^9$/L or the platelet count was between 50 – 100 x 10^9/L. If the platelet count fell below 50 x 10^9/L and/or the ANC fell below 0.5 x 10^9/L, the dose of carboplatin was reduced to an AUC of 5 and Docetaxel was withheld. G-CSF was permitted in patients with Grade 3 or 4 neutropenia.

Reference: Samlowski WE, et al. *Cancer Invest* 2007;25:182 – 8.

DOCETAXEL – CISPLATIN

Docetaxel‡	75 mg/m²	IV*	Day 1
	Followed by		
Cisplatin	75 mg/m²	IV**	Day 1

‡Routine premedication administered; *Administer over 1 hour; **Administer over 30 minutes with adequate pre- and post-hydration.

Repeat cycle every 21 days to a maximum of 12 months.

Reference: Glisson BS, et al. *J Clin Oncol* 2002;20:1593 – 9.

DOCETAXEL – CISPLATIN – 5-FLUOROURACIL (DCF OR TPF)

Docetaxel‡	75 mg/m²	IV*	Day 1
	Followed by		
Cisplatin	75 mg/m²	IV**	Day 1
	Followed by		
5-Fluorouracil	750 mg/m²/day	CIVI	Days 1 – 5

‡Routine premedication administered; *Administer over 1 hour; **Administer with adequate pre- and post-hydration.

Repeat cycle every 21 days for 3-4 cycles then proceed to definitive surgery or radiation therapy.

References: Calais G, et al. *Proc Am Soc Clin Oncol* 2006;24(18S). [Abstract 5506].; Remenar E, et al. *Proc Am Soc Clin Oncol* 2006;24(18S). [Abstract 5516]; FDA Approved Package Insert – http://www.fda.gov/cder/foi/label/2006/020449s039lbl.pdf

PPF (PACLITAXEL – CISPLATIN – 5-FLUOROURACIL)

Paclitaxel‡	175 mg/m²	IV*	Day 1
Cisplatin	100 mg/m²	IV**	Day 2
5-Fluorouracil	500 mg/m²/day	CIVI***	Days 2 – 6

‡Routine premedication administered; *Administer over 3 hours; **Administer over 1 hour with adequate pre- and post-hydration; ***Administer as a continuous 24 hour infusion daily for 5 days.

Repeat cycle every 21 days to a maximum of 3 cycles, and then proceed to definitive radiation ± surgery.

Reference: Hitt R, et al. *Ann Oncol* 2002;13:1665 – 73.

TIC (PACLITAXEL – IFOSFAMIDE – CARBOPLATIN)

Paclitaxel‡	175 mg/m²	IV*	Day 1
Ifosfamide	1000 mg/m²/day	IV**	Days 1 – 3
Mesna	200 mg/m²***	IV	Days 1 – 3
Mesna	400 mg/m²#	IV	Days 1 – 3
Carboplatin	AUC 6	IVΦ	Day 1

‡Routine premedication administered; *Administer over 3 hours; **Administer over 2 hours; ***Administer this dose prior to each dose of ifosfamide; #Administer this dose after each dose of ifosfamide; ΦAUC calculated using the Calvert formula.

NOTE: Consider definitive local treatment with radiation ± surgery after 4 cycles.

Repeat cycle every 21 – 28 days.

References: Shin DM, et al. *Cancer* 2002;95:322 – 30; Shin DM, et al. *Cancer* 2001;91:1316 – 23.

TIP (PACLITAXEL – IFOSFAMIDE – CISPLATIN)

Paclitaxel‡	175 mg/m²	IV*	Day 1
Ifosfamide	1000 mg/m²/day	IV**	Days 1 – 3
Mesna	400 mg/m²/day***	IV	Days 1 – 3
Mesna	200 mg/m²/day#	IV	Days 1 – 3
Cisplatin	60 mg/m²	IVΦ	Day 1

‡Routine premedication administered; *Administer over 3 hours. Hydrate with at least 1000 mL saline over 3 hours prior to paclitaxel; **Administer over 2 hours; ***Administer this dose prior to each dose of ifosfamide; #Administer this dose after each dose of ifosfamide; ΦPre- and post-hydration administered.

Repeat cycle every 21 – 28 days.

Reference: Shin DM, et al. *J Clin Oncol* 1998;16:1325 – 30.

NASOPHARYNGEAL CANCER

CETUXIMAB – CARBOPLATIN

Cetuximab‡	400 mg/m^2	IV	Day 1
Cetuximab‡	250 mg/m^2	IV	Day 8 and weekly thereafter
Carboplatin	AUC 5**	IV	Day 1

‡Routine premedication administered; **AUC according to the Calvert Formula.

DOSE MODIFICATIONS: If a patient experienced Grade 3 skin toxicity, cetuximab therapy could be interrupted for up to 2 consecutive infusions with no change in the dose level. If toxicity resolved to grade 2 or less after up to 2 weeks of interruption, treatment could be resumed. On the 2nd and 3rd occurrence of Grade 3 skin toxicity, cetuximab therapy could be interrupted again for up to 2 consecutive weeks, with subsequent dose reductions to 200 and 150 mg/m^2 respectively. Patients had treatment discontinued if more than 2 consecutive infusions were withheld or if a 4th occurrence of grade 3 skin toxicity occurred. Cetuximab was not held for carboplatin-related toxicities.

Repeat cycle every 21 days to a maximum of 8 cycles.

Reference: Chan AT, et al. *J Clin Oncol* 2005;23:3568 – 76.

CISPLATIN – 5-FLUOROURACIL – RADIATION (INTERGROUP STUDY 0099)

CHEMORADIOTHERAPY FIRST

Cisplatin	100 mg/m^2	IV*	Days 1, 22 and 43

Concurrent with

Radiation	1.8 – 2 Gy fractions Monday to Friday for 35 to 39 fractions for a total dose of 70 Gy.		

POSTRADIOTHERAPY: 4 WEEKS POST RADIATION THERAPY OR LAST DOSE OF CHEMOTHERAPY

Cisplatin	80 mg/m^2	IV*	Day 1
5-Fluorouracil	1000 mg/m^2/day	CIVI	Days 1 – 4

Repeat cycle every 28 days for 3 courses.

*Administer over 15 – 20 minutes with routine pre- and post-hydration.

Reference: Al-Sarraf M, et al. *J Clin Oncol* 1998;16:1310 – 17.