Nimotuzumab in HNSCC

Updates on the current evidences

Innokeys

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nimotuzumab 50 mg

CIMaHer Product Profile

Brand Name	**CIMaHer**
Composition	Vial contain: Nimotuzumab 50 mg
Dosage Form	Injection
Manufacturer	Centro De Inmunologia Molecular (CIM), La Habana, Cuba
Mechanism of Action	Anti EGFR

Nimotuzumab (Indonesia)

Squamous Cell Carcinoma of the Head and Neck

SCCHN

Includes squamous cancers of the mouth, hypopharynx, larynx, pharynx, paranasal sinuses and nasal cavity, and salivary glands[a]

SCCHN by the numbers in 2021[b]

- About 600,000 new cases worldwide
- Estimated new cases in the United States: 54,010 new cases
- Estimated deaths in the United States: 10,850
- ~45% of patients have regional lymph node metastasis at time of diagnosis

Most common etiologic factors[a]:

- Alcohol and tobacco abuse
- HPV infection

HPV, human papillomavirus.

a. NCCN. Head and Neck Cancers (v1.2022). 2022. Accessed February 11, 2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437;
b. Siegel RL, et al. CA Cancer J Clin. 2021;71:7-33.

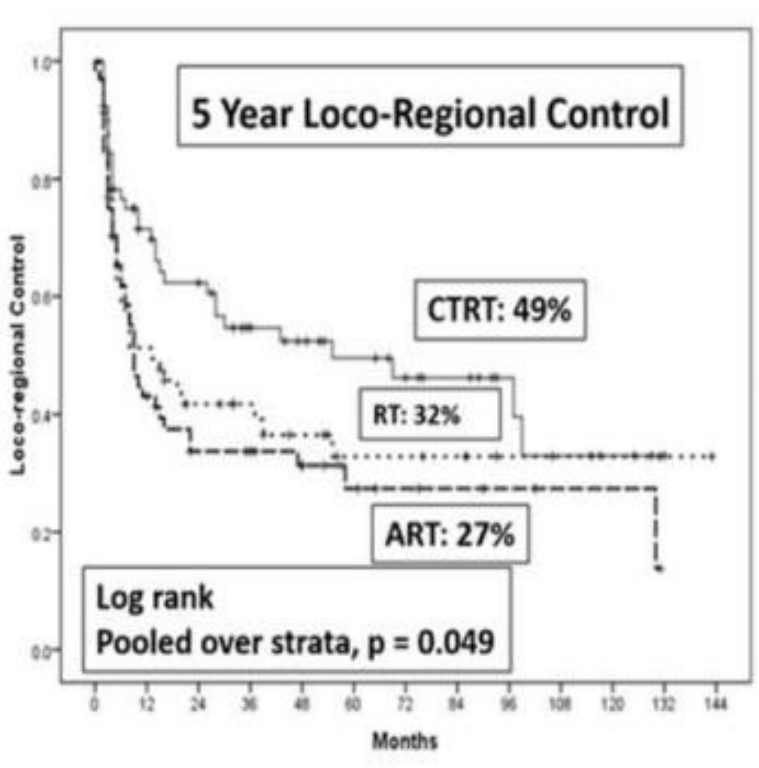
PFS in Chemoradiation

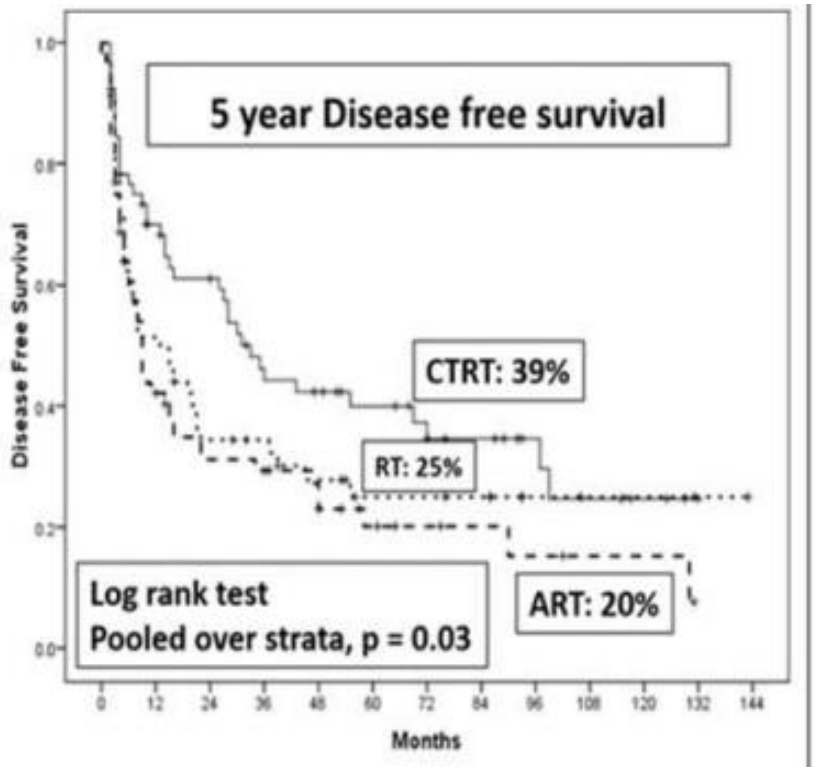
- Chemoradiation is a common treatment strategy but needs future strategies to improve outcome

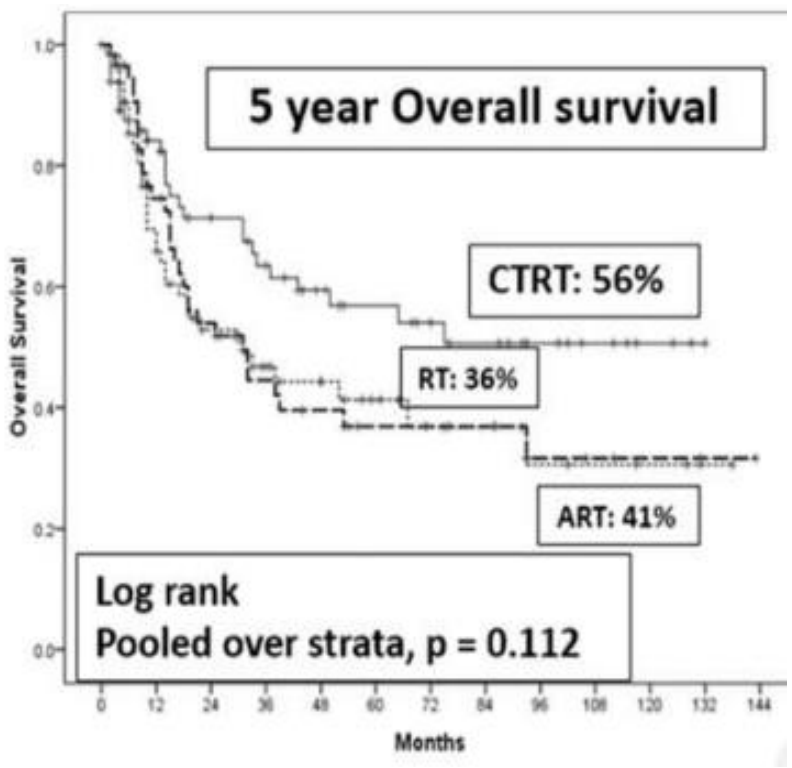
Study	Concurrent chemotherapy	PFS with radiation alone arm	PFS with chemoradiation
Adelstein et al	Cisplatin 100 mg/m2, 3 weekly	14 months	19 months
Budach et al	Mitomycin and 5 FU	11 months	16 months
Denis et al	Carboplatin and 5 FU, 3 weekly	12 months	14 months
Ghosh-Laskar et al	Cisplatin 30 mg/m2, weekly	12 months	24 months

Adelstein et al. J Clin Oncol. 2003 Jan 1;21(1):92-8
Budach et al. J Clin Oncol. 2005 Feb 20;23(6):1125-35
Denis et al. J Clin Oncol. 2004 Jan 1;22(1):69-76.
Ghosh-Laskar et al. Head Neck. 2016 Feb;38(2):202-7.

OS Benefit in Chemoradiation







RT = conventional radiotherapy
CTRT = concurrent chemoradiotherapy
ART = accelerated RT

Ghosh-Laskar et al. Head Neck. 2016 Feb;38(2):202-7

Efforts for improvement

- Neoadjuvant- adjuvant chemotherapy, altered radiation schedules or addition of second chemotherapeutic to cisplatin
  - Failed to improve outcomes
- **EGFR overexpression**
  - Common in HNSCC and confers poor prognosis
  - Addition cetuximab
    - Radiation- improved overall survival
    - Palliative chemotherapy-improved overall survival

Pignon et al. Radiother Oncol. 2009 Jul;92(1):4-14
Ang et al. J Clin Oncol. 2014 Sep 20;32(27):2940-50.
Grandis et al. Cancer Res. 1993 Aug 1;53(15):3579-84.
Bonner et al. N Engl J Med. 2006 Feb 9;354(6):567-78
Vermorken et al. N Engl J Med 2008; 359:1116-1127

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A Randomized Phase 3 Trial Comparing Nimotuzumab Plus Cisplatin Chemoradiotherapy Versus Cisplatin Chemoradiotherapy Alone in Locally Advanced Head and Neck Cancer

Vijay Maruti Patil, MD[1]; Vanita Noronha, MD[1]; Amit Joshi, MD[1]; Jaiprakash Agarwal, MD[2]; Sarbani Ghosh-Laskar, MD [2]; Ashwini Budrukkar, MD[2]; Vedang Murthy, MD[2]; Tejpal Gupta, MD [2]; Manoj Mahimkar, MD[3]; Shashikant Juvekar, MD[4]; Supreeta Arya, MD[4]; Abhishek Mahajan, MD[4]; Archi Agarwal, MD[5]; Nilendu Purandare, MD[5]; Venkatesh Rangarajan, MD[5]; Arun Balaji, MASLP[6]; Sameer Vasant Chaudhari, MD[7]; Shripad Banavali, MD[1]; Sadhana Kannan, MD[8]; Atanu Bhattacharjee, PhD[9]; Anil K. D'Cruz, MS[10]; Pankaj Chaturvedi, MS [10]; Prathamesh S. Pai, MS[10]; Devendra Chaukar, MS[10]; Gouri Pantvaidya, MS[10]; Deepa Nair, MS[10]; Sudhir Nair, MS[10]; Anuja Deshmukh, MS[10]; Shivakumar Thiagarajan, MS[10]; Vijayalakshmi Mathrudev, MBA[1]; Aparna Manjrekar, PGDCR[1]; Sachin Dhumal, MSc[1]; Kamesh Maske, PGDCR[1]; Arti Sanjay Bhelekar, MSc[1]; Kavita Nawale, MBA[1]; Arun Chandrasekharan, MD[1]; Nikhil Pande, MD[1]; Alok Goel, MD[1]; Vikas Talreja, MD[1]; Vijai Simha, MD[1]; Sujay Srinivas, MD[1]; Rohit Swami, MD[1]; Dilip Harindran Vallathol, MD[1]; Hollis Dsouza, MD[1]; Sameer Shrirangwar, MD[1]; Siddharth Turkar, MD[1]; George Abraham, MD[1]; Aditi Harsh Thanky, MD[1]; Usha Patel, MSc[3]; Manish Kumar Pandey, MSc[3]; and Kumar Prabhash, MD [1]

Patil VM et al. Cancer. (2019) 125:3184– 97. doi: 10.1002/cncr.32179

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Trial Design (N=536)

ELIGIBILITY CRITERIA
- Age ≥ 18 years
- SCC of oral cavity/ oropharynx/ hypopharynx/ larynx
- Stage III / IV, no distant metastasis
- Definitive CRT
- Adequate organ function

Stratify
- T-group (T0,1,2 vs T3,4)
- N-group (N0,1 vs N2,3)
- Site (Oropharynx versus non oropharynx)
- Technique of radiation (conventional versus others)

Randomized 1:1 Open Label

Nimotuzumab (200mg) - weekly cisplatin 30mg/m^2 with of RT (NCRT)

Weekly cisplatin 30mg/m^2 with RT (CRT)

Follow-up: Weekly during CRT, then Q3 months x 2 years, then Q6 monthly

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Chemotherapy compliance

Variable	Cisplatin - Radiotherapy arm	Nimotuzumab-cisplatin - Radiotherapy arm	P value
Median number of cisplatin cycles	7 (IQR 7-7)	7 (IQR 7-7)	0.389
Proportion of patients receiving ≥7 cycles cisplatin	219 (81.7%)	226 (84.3%)	0.421
Proportion of patients requiring cisplatin dose reduction	21 (7.8)	26 (9.7)	0.445
Proportion of patients with ≥ 200 mg/m2 of cisplatin	211 (78.7%)	208 (77.6%)	0.754
Median number of Nimotuzumab cycles	Not applicable	7 (IQR 7-7)	-
Proportion of patients receiving ≥7 cycles Nimotuzumab	Not applicable	226 (84.3%)	-

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Radiation compliance

Variable	Cisplatin - Radiotherapy arm	Nimotuzumab-cisplatin - Radiotherapy arm	P value
Median radiotherapy dose	70 Gy (IQR 70-70Gy)	70 Gy (IQR 70-70 Gy)	0.713
100 % of planned radiotherapy dose completed	252 (94.0%)	250 (93.3%)	0.723
Conventional IMRT Not received	229 (85.4%) 38 (14.2%) 1 (0.4%)	238 (88.8%) 29 (10.8%) 1 (0.4%)	0.240
Time for completion of radiation	51 (IQR 49-54)	51 (IQR 49-54)	0.630
Radiation completion time > 63 days	7 (2.6%)	5 (1.9%)	0.559
Proportion of patients with gaps greater than 2 days	72 (26.9%)	80 (29.9%)	0.443
Median cumulative duration of gap	5 (IQR 3-9)	5 (IQR 3-8)	0.824

PFS

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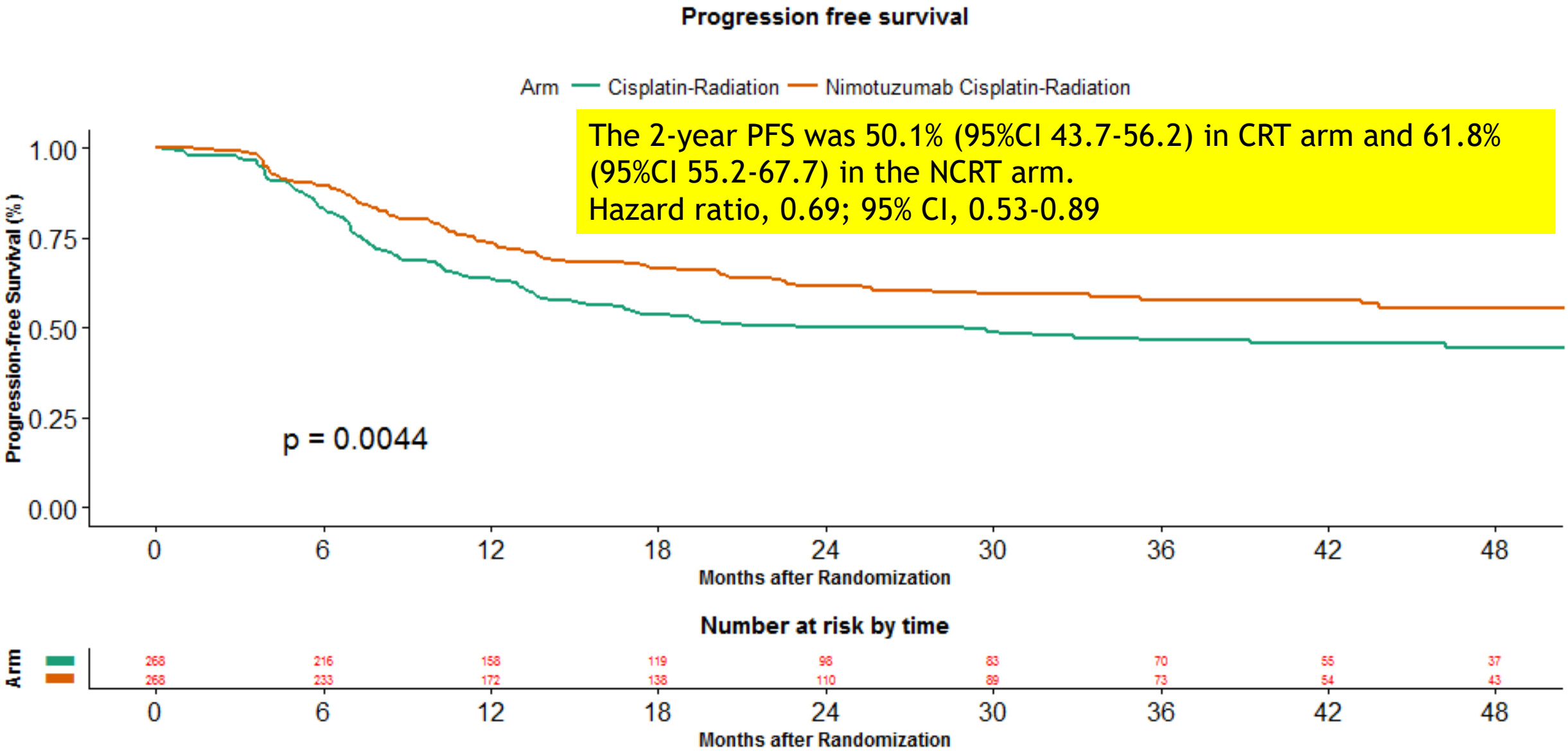
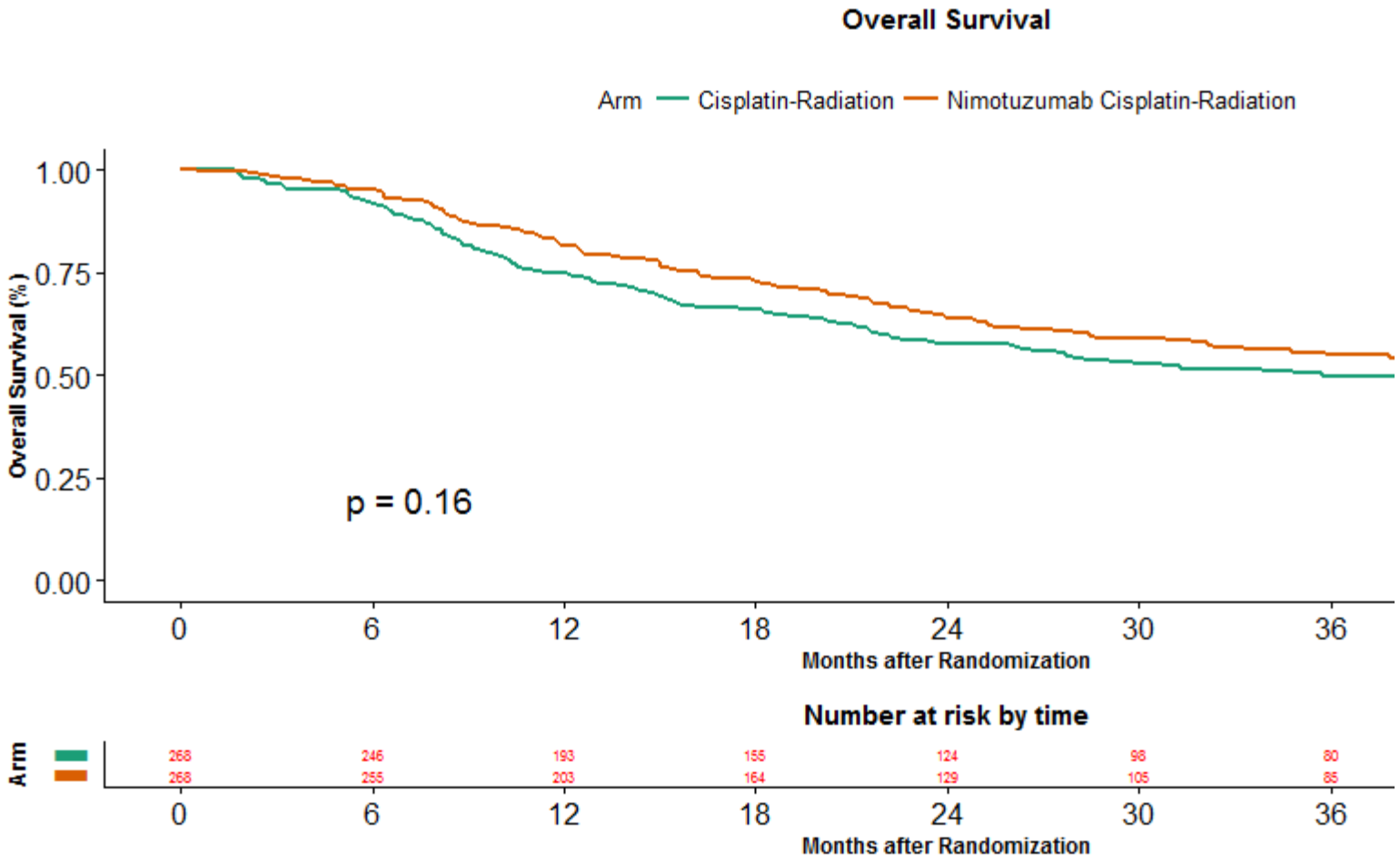


OS

- The hazard ratio in favor of NCRT arm was 0.84, **suggesting a 16% reduction in the risk of death** (95% CI 0.62-1.13) but was not statistically significant.



Comparison between nimotuzumab and cetuximab Phase III clinical trials in combination with chemotherapy and radiotherapy for the treatment of locally advanced head and neck cancer.

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	Nimotuzumab SCCHN	Cetuximab RTOG0522
Number of patients	536 newly diagnosed, stage III or IV locally advanced squamous cell carcinomas	891 stage III or IV (T2N2-3M0 or T3-4, any N, M0) squamous cell carcinoma
Primary endpoint	Progression free survival	Progression free survival
P16 positivity	11.3%	73.2%
Treatment schedule	Cisplatin dose: 30 mg/m2 , weekly RT dose: 70 Gy Nimotuzumab dose: 200 mg, weekly for 7 weeks	Cisplatin dose: 100 mg/m2 , on days 1 and 22 of RT. RT dose: 70–72 Gy. Cetuximab dose: 400 mg/m2 (induction), then 250 mg/m2 weekly for 7 weeks.
Treatment compliance	No differences in radiotherapy interruption between arms. Radiotherapy interruptions as a result of toxicity was 4.5% in the nimotuzumab arm vs. 3.7% in the control arm.	Radiotherapy interruption as a result of toxicity was significantly higher in the cetuximab vs. control arm (26.9 vs. 15.1%) $p < 0.001$).
Efficacy	Significant improvement in PFS, locoregional control, and disease-free survival with nimotuzumab. Trend toward improved survival.	No significant differences between arms in PFS, overall survival, locoregional failure, or distant metastases.
Safety	Grade 3–5 adverse events were similar between the 2 arms, except for a higher incidence of mucositis in the nimotuzumab vs. control arm (66.7 vs. 55.8%; $p = 0.01$).	Cetuximab arm had significantly higher rates of grade 3–4 skin reactions, radiation mucositis, fatigue, anorexia, and hypokalemia up to 90 days from the start of therapy

2024 ASCO ANNUAL MEETING

Long term results of a randomized phase III study of nimotuzumab in combination with concurrent radiotherapy and cisplatin versus radiotherapy and cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck.

Professor Vijay Maruti Patil
On behalf of Department of Medical Oncology
Head and Neck DMG
Tata Memorial Centre, Mumbai

Background

- Addition of nimotuzumab to weekly cisplatin as radiosensitizer (CTRT) had improved progression free survival(PFS) in a phase 3 study in locally advanced head and neck squamous cell carcinoma (LAHNSCC). [1]
- Whether it leads to an improvement in long term OS is unknown.
- This analysis was performed to evaluate the 10-year OS and late term adverse events of the addition of nimotuzumab to CTRT in LAHNSCC.

1. Patil VM, Noronha V, Joshi A, et al. A randomized phase 3 trial comparing nimotuzumab plus cisplatin chemoradiotherapy versus cisplatin chemoradiotherapy alone in locally advanced head and neck cancer. *Cancer*. 2019;125(18):3184-3197. doi:10.1002/cncr.32179

Trial Design

ELIGIBILITY CRITERIA

- Age ≥ 18 years
- SCC of oral cavity/ oropharynx/ hypopharynx/ larynx
- Stage III / IV, no distant metastasis
- Definitive CRT
- Adequate organ function

Stratify

- T-group (T0,1,2 vs T3,4)
- N-group (N0,1 vs N2,3)
- Site (Oropharynx versus non oropharynx)
- Technique of radiation (conventional versus others)

Randomized 1:1 Open Label

n=268 → **Nimotuzumab (200mg) -weekly cisplatin 30mg/m² with of RT (NCRT)**

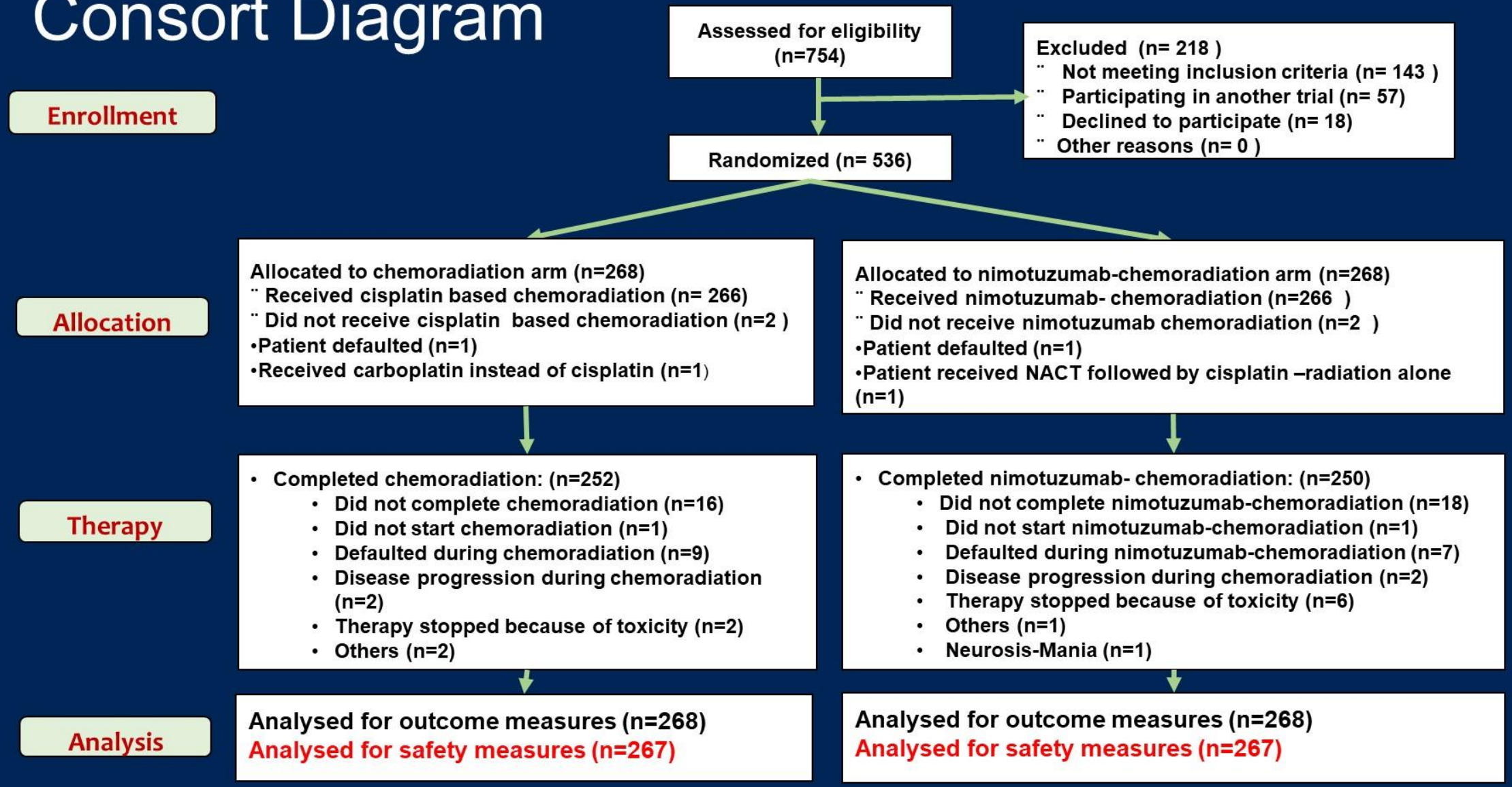
RT: 70 Gy/35# /-7 weeks

n=268 → **Weekly cisplatin 30mg/m² with RT (CRT)**

Primary endpoint: 10-year overall survival
Key secondary endpoint: Late adverse events

PRESENTED BY: Professor Vijay M Patil

Consort Diagram

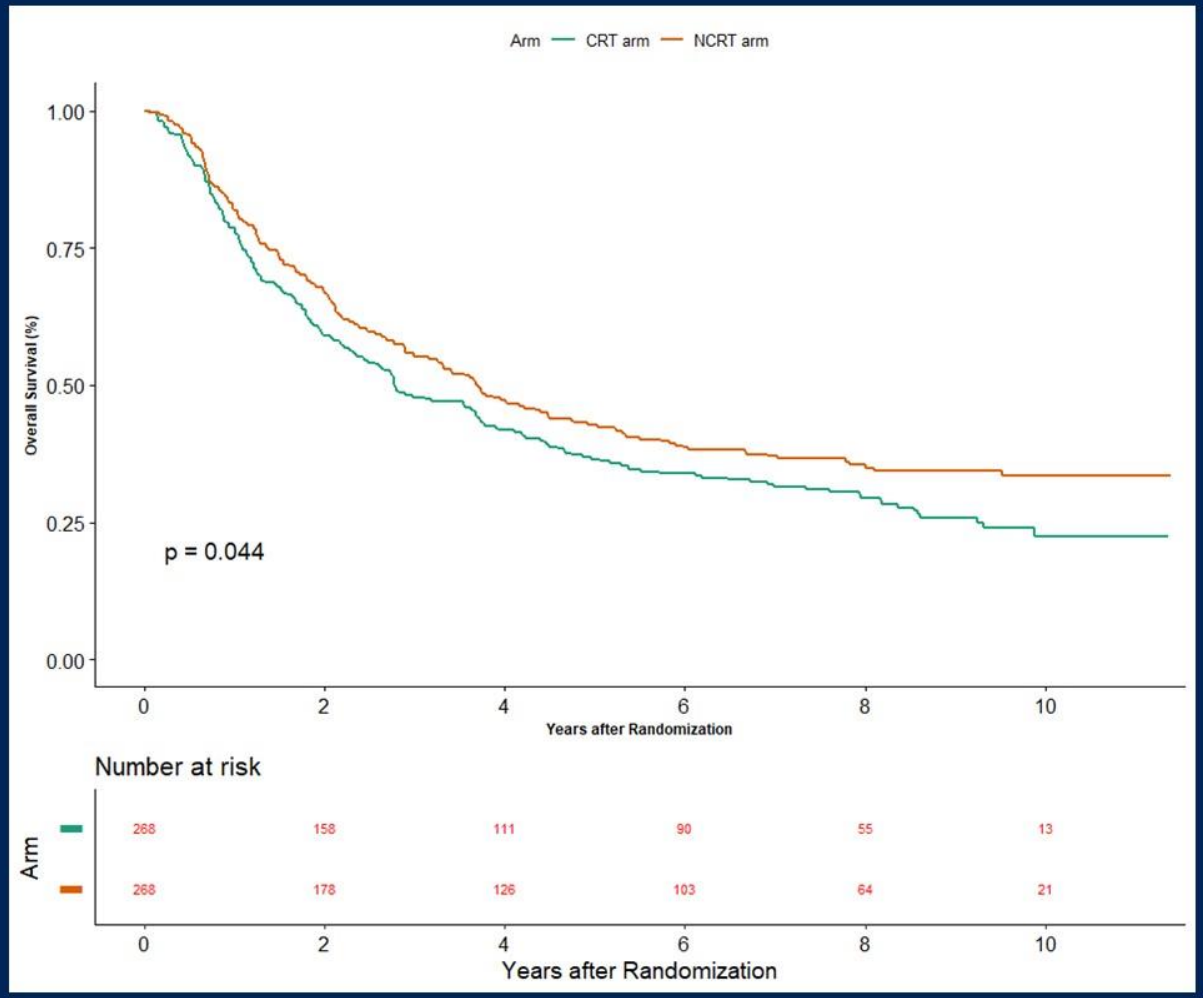


Baseline characteristics

Variable	Cisplatin - Radiotherapy arm	Nimotuzumab-cisplatin - Radiotherapy arm	P value
Median age	54.00 (26-77 years)	55.00 (20-73 years)	0.636
ECOG PS 0-1 ECOG PS 2	267 (99.6%) 1 (0.4%)	267 (99.6%) 1 (0.4%)	1
Oropharynx Hypopharynx Larynx Oral cavity	135 (50.4) 47 (17.5) 83 (31) 3 (1.1)	134 (50) 62 (23.1) 72 (26.9) 0 (0)	0.119
T0-T2 T3-T4	56 (20.9%) 212 (79.1%)	41 (15.3%) 227 (84.7%)	0.113
N0-N1 N2-N3	131 (48.9%) 137 (51.1%)	122 (45.5%) 146 (54.5%)	0.488
Stage III Stage IVA Stage IV B	87 (32.5%) 172 (64.2%) 9 (3.4%)	80 (29.9%) 177 (66.0%) 11 (4.1%)	0.753
HPV positive **HPV negative** **HPV equivocal**	14 (10.4) 91 (67.4) --	10 (7.5) 96 (71.6) 1 (0.7)	.517

OS (overall)

- The median OS was 2.78 years (95% CI 2.31-3.69) versus 3.69 years (95% CI 2.90-4.49) in the CRT and NCRT arm respectively (P value by log rank test=0.04).
- The 10 year OS was 22.5% (95% CI 16.7-28.8) versus 33.5% (95% CI 27.6-39.4) in the CRT and NCRT arm respectively (Hazard ratio=0.811; 95%CI 0.664-0.995, P=0.044).



Adverse events

Variable	Cisplatin - Radiotherapy arm		Nimotuzumab-cisplatin - Radiotherapy arm		P value
	All Grades	Grade 2 and above	All Grades	Grade 2 and above	Grade 2 and above
Shoulder	191 (100%)	184 (96.3%)	191 (100%)	184 (97.4%)	0.771
Xerostomia	185 (96.9%)	137 (71.7%)	178 (94.2%)	122 (64.6%)	0.152
Pigmentation	176 (92.1%)	29 (15.2%)	170 (89.9%)	32 (16.9%)	0.677
Skin thickening	180 (94.2%)	102 (53.4%)	174 (92.1%)	101 (53.4%)	1.000
Dysphagia	78 (40.8%)	18 (9.4%)	76 (40.2%)	25 (13.2%)	0.260
Dysgeusia	150 (78.5%)	53 (27.7%)	139 (73.5%)	47(24.9%)	0.561
Hypothyroidism	78 (40.8%)	38 (19.9%)	84 (44.4%)	47 (24.9%)	0.269
Hypercholesterolemia	47 (24.6%)	0 (0%)	40 (21.2%)	1 (0.5%)	0.497
Hearing loss	28 (14.7%)	17 (8.9%)	23 (12.2%)	12 (6.3%)	0.440
Increased creatinine	11 (5.8%)	3 (1.6%)	6 (3.2%)	1 (0.5%)	0.623

Conclusion

- Addition of nimotuzumab to weekly cisplatin leads to improvement in long term overall survival in locally advanced HNSCC without any additional increase in late-term adverse events.
- These results are largely applicable in HPV negative patients.

Acknowledgements

Patients and their families

Statistics & Randomization
Sadhana Kannan
Kumar Prabhash
Atanu Bhattacharjee

Funding: Biocon ltd & TRAC

Head and Neck DMG

Thank you

Systematic Review and Network Meta Analysis for LA-HNSCC

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Locally advanced head and neck squamous cell carcinoma treatment efficacy and safety: a systematic review and network meta-analysis

Huanhuan Wang[1,2], Zhuangzhuang Zheng[1,2], Yangyu Zhang[3], Chenbin Bian[1,2], Jindian Bao[1,2], Ying Xin[4,5]* and Xin Jiang[1,2]*

[1]Jilin Provincial Key Laboratory of Radiation Oncology and Therapy, The First Hospital of Jilin University, Changchun, China, [2]NHC Key Laboratory of Radiobiology, School of Public Health, Jilin University, Changchun, China, [3]Division of Clinical Research, The First Hospital of Jilin University, Changchun, China, [4]Key Laboratory of Pathobiology, Ministry of Education, Jilin University, Changchun, China , [5]College of Basic Medical Sciences, Jilin University, Changchun, China

Summary of Studies

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- CCRT (cisplatin + nimotuzumab + RT) and nimotuzumab concurrent with RT have **significant advantages in both efficacy and long-term survival** compared with various conventional LA-HNSCC treatment regimens, including platinum-based CCRT regimens (including cisplatin and carboplatin).
- At the same time, it was surprising that CCRT (cisplatin + nimotuzumab + RT) and nimotuzumab concurrent with RT **did not cause** a higher proportion of ≥3 AEs than most combination regimens.
- **This suggests that CCRT (cisplatin + nimotuzumab + RT) and nimotuzumab combined with RT may be the most promising treatment option for LAHNSCC.**
- The efficacy and safety advantages of CCRT (cisplatin + nimotuzumab + RT) and nimotuzumab concurrent with RT regimens warrant a higher-level recommendation by the NCCN guidelines
- Cetuximab concurrent with RT regimen as an alternative to platinum-based chemotherapy **did not show a better advantage in OS, PFS, and DSS**. In addition, cetuximab concurrent with RT regimen was associated with a higher rate of ≥3 AEs than RT, suggesting that the recommendation grade in future NCCN guidelines needs to be adjusted or removed

Systematic Review of R/M SCCHN Treatment Options

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Systemic Therapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma- A Systematic Review and Meta-Analysis

Ashley Lau, Wei-fa Yang, Kar-Yan Li, Yu-xiong Su*

Department of Oral and Maxillofacial Surgery, Prince Phillip Dental Hospital, 34 Hospital Road, Sai Ying Pun, Hong Kong Special Administrative Region

In summary, **IMT (Immunotherapy) appears to be paving the frontier of R/M HNSCC treatment** but its routine use is hindered by its **expense and the challenge of selecting patients who will truly benefit**. **EGFR inhibitors may remain a reasonable choice** for those not eligible for IMT; however systemic therapy should ultimately employ **an individualized approach** to optimize treatment outcomes.

Clinical Evidences of Nimotuzumab for R/M SCCHN

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Original Article

Efficacy and tolerability of nimotuzumab in combination with chemotherapy in recurrent and metastatic squamous cell carcinoma of head and neck at a cancer center in Northern India

Abhishek Yadav, Pankaj Goyal, Chaturbhuj R Agrawal, Sneha J Bothra, Parveen Jain, Kumardeep Dutta Choudhury, Sunil Kumar Gupta, Manish Sharma, Rajat Bajaj, Amitabh Upadhyay, Prashanta Dash, Dinesh C Doval

Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Correspondence to: Chaturbhuj R Agrawal, E-mail: chaturbhujagrawal06@rediffmail.com

Prospective, Interventional, Non-Randomized, Comparative Study
N = 124 patients

Study design

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NIMOTUZUMAB ARM	CONTROL ARM
Nimotuzumab weekly 200 mg + paclitaxel 135-175 mg/m^2 or docetaxel 75 mg/m^2 + cisplatin 60-75 mg/m^2 or carboplatin AUC 5) 3 weekly	Paclitaxel 135-175 mg/m^2 or docetaxel 75 mg/m^2 + cisplatin 60-75 mg/m^2 or carboplatin AUC 5, 3 weekly

Standard treatment was defined as six cycles, unless there was disease progression or unacceptable toxicity

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Result

Response	Nimotuzumab Arm n (%)	Control Arm n (%)
Complete response	2 (3.6%)	2 (3.4%)
Partial response	19 (34.5%)	9 (15.5%)
Stable disease	20 (36.4%)	14 (24.1%)
Disease progression 33 (56.9%)	14 (25.5%)	33 (56.9%)
ORR (CR + PR) 11 (19%)	21 (38.2%)	11 (19%)
Disease control rate (CR + PR + SD)	35 (74.5%)	25 (43.1%)

Nimotuzumab improve overall response rate

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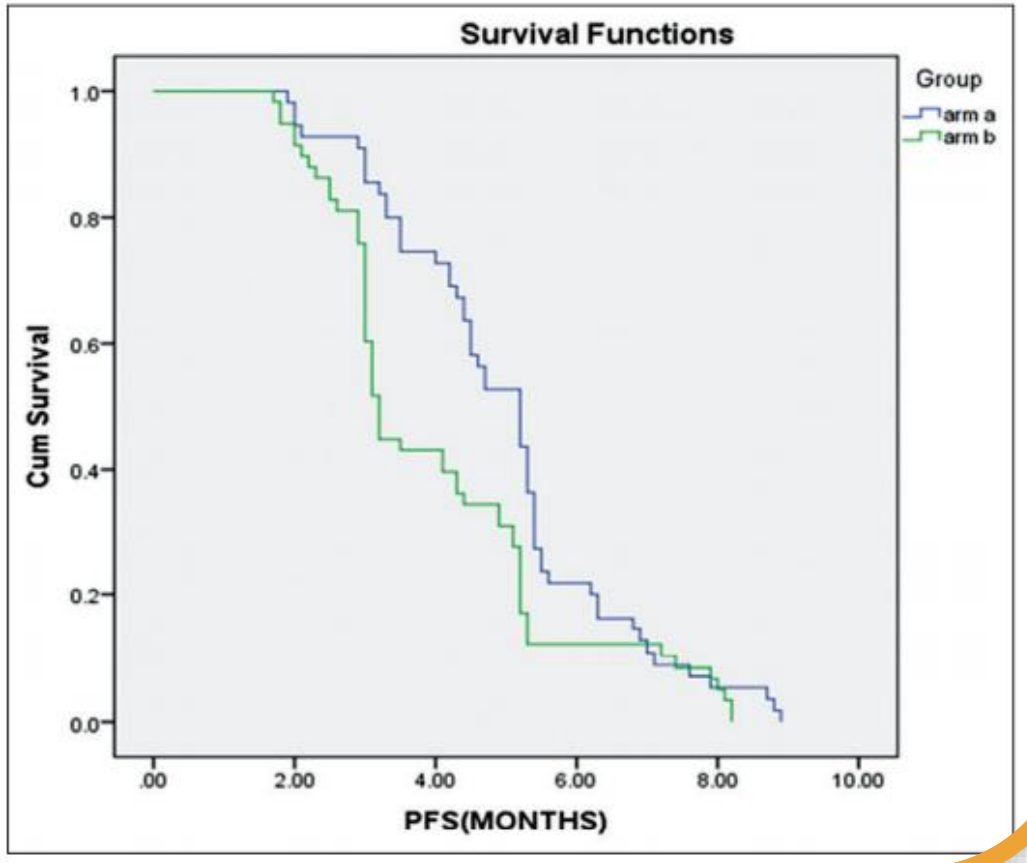
Progression Free Survival



PFS = 5.2 months vs 3.2 months
***p* = 0.00763**

Toxicity

Table 4: Overall grades 3 and 4 toxicities

Grade 3-4 toxicity	Arm A No of patients (%)	Arm B No of patients (%)
Anemia	15 (27.3%)	13 (22.4%)
Neutropenia	19 (35.5%)	20 (34.5%)
Thrombocytopenia	10 (18.2%)	9 (15.5%)
Leucopenia	20 (36.4%)	23 (39.7%)
Febrile Neutropenia	4 (7.2%)	7 (8.6%)
Skin rashes	0 (0%)	0 (0%)
Hypomagnesemia	1 (1.8%)	0 (0%)
Hypokalemia	2 (3.6%)	2 (3.4%)
Hyponatremia	1 (1.8%)	2 (3.4%)
GI and mucositis	14 (25.5%)	13 (22.4%)
Neuropathy	3 (5.5%)	2 (3.4%)
Infection	6 (10.9%)	8 (13.8%)
Cardiac	1 (1.8%)	2 (3.4%)
Renal	1 (1.8%)	2 (3.4%)
Infusion reaction	2 (3.6%)	1 (1.7%)

Table 6: Anti-EGFR monoclonal antibody-related grade 3-4 toxicities

Grade 3-4 toxicity	EXTREME trial[14] (Cetuximab + CT)	SPECTRUM trial[15] (Panitumumab + CT)	Present study
Skin	9%	19%	0%
Cardiac	7%	8%	1.8%
Hypomagnesemia	5%	12%	1.8%
Hypokalemia	7%	10%	3.6%

The addition of Nimotuzumab to chemotherapy did not add on to toxicity.
The excellent safety profile has been observed.

Comparison with other studies

Table 5: Clinical trials of anti-EGFR monoclonal antibody plus chemotherapy in R/M SCCHN

Trial	Monoclonal antibody	Chemotherapy regime	Response rate (%)	Median PFS
Vermorken *et al*. (EXTREME trial)[14]	Cetuximab	Platinum/5 FU	36.0 vs. 20.0	5.6 vs. 3.3 months ($P<0.001$)
Vermorken *et al*. (SPECTRUM trial)[15]	Panitumumab	Platinum/5 FU	37.0 vs. 26.0	5.8 vs. 4.6 months ($P=0.0036$)
Present study	Nimotuzumab	Platinum/taxane	38.2 vs. 19.0	5.2 vs. 3.2 months ($P=0.009$)

Platinum=Cisplatin/carboplatin, Taxane=Paclitaxel/docetaxel

The major finding in our study was that **nimotuzumab displayed efficacy without producing clinically significant toxicity** which is typical to other monoclonal antibodies. It is **very well tolerated** due to its **excellent safety profile** with **good compliance to treatment.**

Thank you