clinical trial updates

Final Overall Survival Analysis of Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma: A Multicenter, Randomized Phase III Trial

Yuan Zhang, MD, PhD[1]; Lei Chen, MD, PhD[1]; Guo-Qing Hu, MD[2]; Ning Zhang, MD[3]; Xiao-Dong Zhu, MD, PhD[4]; Kun-Yu Yang, MD[5]; Feng Jin, MD[6]; Mei Shi, MD, PhD[7]; Yu-Pei Chen, MD[1]; Wei-Han Hu, MD[1]; Zhi-Bin Cheng, MD[8]; Si-Yang Wang, MD[9]; Ye Tian, MD[10]; Xi-Cheng Wang, MD[11]; Yan Sun, MD, PhD[12]; Jin-Gao Li, MD[13]; Wen-Fei Li, MD, PhD[1]; Yu-Hong Li, MD[14]; Yan-Ping Mao, MD, PhD[1]; Guan-Qun Zhou, MD, PhD[1]; Rui Sun, MD[1]; Xu Liu, MD, PhD[1]; Rui Guo, MD, PhD[1]; Guo-Xian Long, MD, PhD[2]; Shao-Qiang Liang, MD[3]; Ling Li, MD, PhD[4]; Jing Huang, MD, PhD[5]; Jin-Hua Long, MD[6]; Jian Zang, MD[7]; Qiao-Dan Liu, MD, PhD[9]; Li Zou, MD, PhD[10]; Qiong-Fei Su, MD[11]; Bao-Min Zheng, MD, PhD[12]; Yun Xiao, MD[13]; Ying Guo, PhD[15]; Fei Han, MD, PhD[1]; Hao-Yuan Mo, MD[16]; Jia-Wei Lv, MD[1]; Xiao-Jing Du, MD, PhD[1]; Cheng Xu, MD, PhD[1]; Na Liu, MD, PhD[1]; Ying-Qin Li, MD, PhD[1]; Fang-Yun Xie, MD[1]; Ying Sun, MD, PhD[1]; Jun Ma, MD[1]; and Ling-Long Tang, MD, PhD[1]

abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically on the based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

We previously reported significantly improved failure-free survival using gemcitabine plus cisplatin induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma. Here, we present the final overall survival (OS) analysis. In this multicenter, randomized trial, patients were assigned to be treated with concurrent chemoradiotherapy alone (standard therapy, n = 238) or gemcitabine and cisplatin induction chemotherapy before concurrent chemoradiotherapy (n = 242). With a median follow-up of 69.8 months, the induction chemotherapy group had a significantly higher 5-year OS (87.9% *v* 78.8%, hazard ratio, 0.51 [95% CI 0.34 to 0.78]; $P = .001$) and a comparable risk of late toxicities (≥ grade 3, 11.3% *v* 11.4%). Notably, the depth of the tumor response to induction chemotherapy correlated significantly and positively with survival (complete response *v* partial response *v* stable/progressive disease, 5-year OS, 100% *v* 88.4% *v* 61.5%, $P = .005$). Besides, patients with a low pretreatment cell-free Epstein-Barr virus DNA load (< 4,000 copies/mL) might not benefit from induction chemotherapy (5-year OS, 90.6% *v* 91.4%, $P = .77$). In conclusion, induction chemotherapy before concurrent chemoradiotherapy improved OS significantly in patients with locally advanced nasopharyngeal carcinoma, without increasing the risk of late toxicities. Tumor response to induction chemotherapy and pretreatment cell-free Epstein-Barr virus DNA might be useful to guide individualized treatment.

J Clin Oncol 40:2420-2425. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Sharing Statement
Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 13, 2022 and published at ascopubs.org/journal/jco on June 16, 2022: DOI https://doi.org/10.1200/JCO.22.00327

INTRODUCTION

Nasopharyngeal carcinoma is distinct from other head and neck cancers for its association with Epstein-Barr virus[1] (EBV) and unbalanced geographical distribution. More than 70% of patients present with locoregionally advanced disease at diagnosis,[2] and concurrent chemoradiotherapy constitutes the backbone of their treatment. Focusing on this unfavorable subgroup of patients, we conducted a randomized trial to investigate the efficacy of the addition of gemcitabine and cisplatin induction chemotherapy. Encouragingly, we found that both failure-free survival (3-year rates: 85.3% *v* 76.5%, $P = .001$) and overall survival (OS; 94.6% *v* 90.3%) improved significantly.[3] Since then, the guidelines of the National Comprehensive Cancer Network have recommended induction chemotherapy as the standard of care (category 1 recommendation) in this setting, with gemcitabine and cisplatin as the preferred regimen.

Here, we reported the prespecified 5-year survival results. In addition, as induction chemotherapy is an emerging strategy for nasopharyngeal carcinoma, evidence of its individualized application is limited. Therefore, we also provided new data to explore effective prognostic or predictive factors, which could be used to guide therapeutic decisions and prognosis evaluation in the clinic.

TABLE 1. Baseline Characteristics

Characteristic	Induction Chemotherapy Group[a] (n = 242)	Standard Therapy Group[a] (n = 238)	*P*
Sex			.12
Male	182 (75.2)	164 (68.9)	
Female	60 (24.8)	74 (31.1)	
Age, years	46 (18-64)	45 (20-64)	
Karnofsky performance status score[b]			.22
100	10 (4.1)	10 (4.2)	
90	189 (78.1)	198 (83.2)	
80	36 (14.9)	21 (8.8)	
70	7 (2.9)	9 (3.8)	
T category[c]			.95
T1	2 (0.8)	3 (1.3)	
T2	16 (6.6)	16 (6.7)	
T3	115 (47.5)	116 (48.7)	
T4	109 (45.0)	103 (43.3)	
N category[c]			.72
N1	114 (47.1)	106 (44.5)	
N2	101 (41.7)	108 (45.4)	
N3A	12 (5.0)	8 (3.4)	
N3B	15 (6.2)	16 (6.7)	
TNM stage[c]			.61
III	111 (45.9)	120 (50.4)	
IVA	105 (43.4)	94 (39.5)	
IVB	26 (10.7)	24 (10.1)	

NOTE. Data are the median (IQR) and No. (%).

Abbreviations: IQR, interquartile range; N, node; T, tumor.

[a]Patients in the induction chemotherapy group received gemcitabine plus cisplatin and concurrent chemoradiotherapy, and patients in the standard therapy group received concurrent chemoradiotherapy alone. There were no significant differences between the treatment groups in the characteristics at baseline.

[b]Karnofsky performance status scores are assessed on a scale from 0 to 100, with lower scores indicating greater disability.

[c]Tumor and node categories and disease stage were assessed according to the seventh edition of American Joint Committee on Cancer—Union for International Cancer Control stage classification system.

METHODS

Study Design and Participants

Study design was detailed in the primary report[3] and the Data Supplement (online only). In brief, we enrolled patients with newly diagnosed, nonmetastatic stage III-IVB disease (excluding T3-4N0, using American Joint Committee on Cancer/Union for International Cancer Control seventh edition[4]). Eligible patients were randomly assigned, stratified by tumor stage (III/IV) and treatment center, to be treated using either gemcitabine and cisplatin induction chemotherapy before concurrent chemoradiotherapy (induction chemotherapy group) or concurrent chemoradiotherapy alone (standard therapy group). The Protocol (online only) was approved by the institutional ethics review boards at all participating centers. Before enrollment, all patients provided written informed consent.

End Points and Assessments

The primary end point was failure-free survival, representing the time from random assignment to documented disease failure (distant or locoregional) or death. OS represented the time from random assignment to death (Data Supplement). Before treatment, the load of plasma cell–free EBV DNA was measured at a central laboratory (Data Supplement). Approximately 1 week after completing induction chemotherapy, tumor responses were assessed radiographically and categorized as complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD; Data Supplement). Late toxicities were graded using the Radiation Therapy Oncology Group's Late Radiation Morbidity Scoring Criteria.[5]

Statistical Analysis

The trial required a sample size of 476 patients.[3] Kaplan-Meier curves were used to present time-to-event data, and

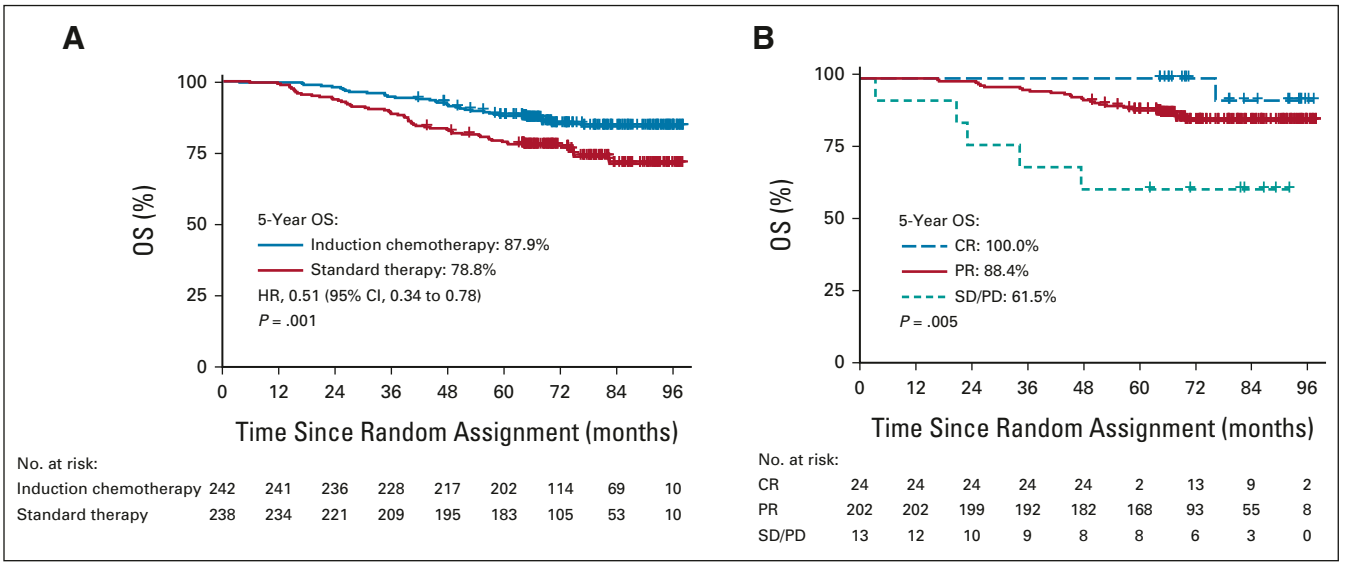

FIG 1. Kaplan-Meier analysis of OS in (A) the intention-to-treat population and (B) stratified by tumor response to induction chemotherapy. A stratified Cox proportional hazards model was used to calculate the HRs and their 95% CIs. Plus symbols indicate censored data. CR, complete response; HR, hazard ratio; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

the two groups were compared using log-rank tests, stratified by disease stage and trial center.[6] The hazard ratios (HRs) and 95% CIs were calculated using a stratified Cox proportional hazards model. Schoenfeld residuals were used to test the proportional hazards assumption.[7] A type I error rate of 0.05 was set; all tests were two-sided. SPSS version 22.0 (IBM, Armonk, NY) was used. The database is preserved at the Research Data Deposit public platform (RDDA2021001967).

RESULTS

Survival Outcomes

A total of 480 patients were randomly assigned—242 to the induction chemotherapy group and 238 to the standard therapy group (Table 1). With a median follow-up of 69.8 months, the patients in the induction chemotherapy group had significantly better 5-year OS (87.9% *v* 78.8%, HR, 0.51 [95% CI, 0.34 to 0.78], $P = .001$; Fig 1A). The Data Supplement shows the detailed breakdown of the causes of death. Although the study did not have sufficient power to test interaction, the improvement of OS was consistent across the different subgroups (Data Supplement).

Both 5-year failure-free survival (81.3% *v* 67.3%, HR, 0.51 [95% CI, 0.36 to 0.73], $P < .001$; Data Supplement) and distant metastasis-free survival (90.0% *v* 77.9%, HR, 0.42 [95% CI, 0.27 to 0.67], $P < .001$; Data Supplement) were higher in the induction chemotherapy group. Notably, the 5-year locoregional recurrence-free survival was numerically higher in the induction chemotherapy group (87.8% *v* 82.9%, HR, 0.65 [95% CI, 0.41 to 1.02], $P = .06$; Data Supplement), despite marginally statistical significance.

Late Toxicities

The occurrence rates of all grades (95.4% *v* 99.2% for induction chemotherapy *v* standard therapy) and ≥ grade 3 (11.3% *v* 11.4%) late toxicities were comparable (Data Supplement). In detail, the most common ≥ grade 3 late toxicities included ear toxicity (7.1% *v* 8.4%), dry mouth (2.9% *v* 2.1%), and trismus (0.4% *v* 1.7%). All types were similar between treatment groups, except for G1-2 peripheral neuropathies (9.2% *v* 1.7%). Besides, three patients (one *v* two) developed secondary malignancies during follow-up.

Prognostic Value of Tumor Response to Induction Chemotherapy

After induction chemotherapy, 10.0% (24 of 239) and 84.5% (202 of 239) of patients achieved complete and PRs, respectively; 4.2% (10 of 239) of patients had SD, and tumors progressed in 1.3% (3 of 239) of patients. The survival outcomes were significantly and positively associated with the depth of response (CR *v* PR *v* SD/PD, 5-year OS, 100% *v* 88.4% *v* 61.5%, $P = .005$, Fig 1B). Patients with SD or PD had more than 12-fold higher risk of death (HR, 12.83 [95% CI, 1.50 to 109.91], $P = .02$) compared with complete responders and more than three-fold higher risk (HR, 3.53 [95% CI, 1.36 to 9.16], $P = .009$) compared with partial responders. Treatment response retained its prognostic value after adjusting for other covariates ($P = .02$).

Predictive Value of Cell-Free Epstein-Barr Virus DNA for Induction Chemotherapy

Overall, 313 (65.2%) patients had pretreatment cell-free Epstein-Barr virus (cfEBV) DNA assay, and the median

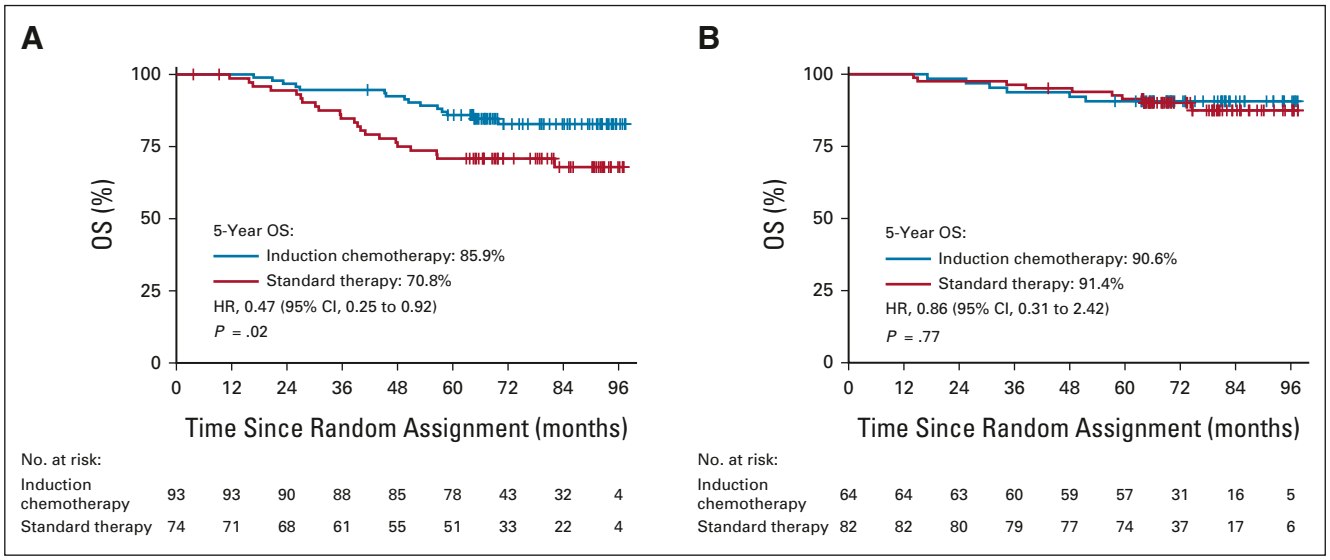

FIG 2. Kaplan-Meier survival curves for OS in the two treatment groups stratified by different pretreatment cell-free EBV DNA loads: (A) ≥ 4,000 and (B) < 4,000 copies/mL. HRs and 95% CIs were calculated using an unstratified Cox proportional hazards model. Plus symbols indicate censored data. EBV, Epstein-Barr virus; HR, hazard ratio; OS, overall survival.

concentration was 4,930 copies/mL. For patients whose pretreatment cfEBV DNA was ≥ 4,000 copies/mL, induction chemotherapy significantly improved their 5-year OS (85.9% *v* 70.8%, *P* = .02, Fig 2A). However, this survival benefit was not observed for patients whose pretreatment cfEBV DNA was < 4,000 copies/mL (90.6% *v* 91.4%, *P* = .77, Fig 2B). Both were confirmed in multivariate analysis (*P* = .04 and *P* = .60, respectively).

DISCUSSION

This landmark analysis provided decisive evidence of the efficacy of gemcitabine and cisplatin induction chemotherapy, which improved the 5-year OS by 9.1% and decreased the relative risk of death by 49%, representing a major improvement in this high-risk group of patients. This efficacy was likely attributed to its efficacy in reducing distant metastasis (HR, 0.42) and its good safety profile. Remarkably, although induction chemotherapy delays initiation of radiotherapy, previously expressed concerns about the increased risk of locoregional recurrence seem to be unfounded.

Importantly, we found that the tumor's response to induction chemotherapy could inform survival outcomes and might guide individualized treatment. For patients who achieved a CR, such extreme sensitivity portends a favorable prognosis and the feasibility of deintensification of the subsequent chemotherapy or radiotherapy,[8] which are being investigated in prospective trials (ClinicalTrials.gov identifier: NCT03668730, etc). Meanwhile, for SD or PD, treatment intensification using drugs with different mechanisms of action, such as the integration of immune checkpoint inhibitors in the concurrent or adjuvant phase or metronomic capecitabine as adjuvant therapy, might help to eliminate these treatment-resistant clones (ClinicalTrials.gov identifier: NCT04072107),[9] given the reported success in the disease.[10-12]

Our results also showed that the pretreatment cfEBV DNA load might be a candidate predictive biomarker for induction chemotherapy. Although induction chemotherapy demonstrated efficacy in the whole population, those with a low EBV DNA load might not benefit. This might be attributed to the favorable prognosis in this subgroup, who have a relatively low disease burden, diminishing the possible benefit of induction chemotherapy. Prospective trials are needed to confirm whether induction chemotherapy could be spared in these patients.

In conclusion, the OS benefit highlights the standard role of gemcitabine and cisplatin induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma. Tumor response to induction chemotherapy and pretreatment cfEBV DNA load were identified as potential factors to guide individualized treatment.

AFFILIATIONS

[1]Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, People's Republic of China
[2]Department of Oncology, Cancer Center, Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[3]Department of Radiation Oncology, The First People's Hospital of Foshan, Foshan, China
[4]Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, China
[5]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[6]Department of Head and Neck Oncology, Affiliated Cancer Hospital of Guizhou Medical University, Guiyang, China
[7]Department of Radiation Oncology, XiJing Hospital of Air Force Medical University, Xi'an, China
[8]The Cancer Center of the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China
[9]Department of Head and Neck Oncology, The Cancer Center of the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China
[10]Department of Radiation Oncology, The Second Affiliated Hospital of Soochow University, Suzhou, China
[11]Department of Radiation Oncology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China
[12]Department of Radiation Oncology, Peking University Cancer Hospital, Beijing, China
[13]Department of Radiation Oncology, Jiangxi Cancer Hospital, Nanchang, China
[14]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China
[15]Clinical Trials Center, Sun Yat-sen University Cancer Center, Guangzhou, China
[16]Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China

CORRESPONDING AUTHOR

Ling-Long Tang, MD, PhD, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, No. 651 Dongfeng Rd East, Guangzhou 510060, China; e-mail: tangll@sysucc.org.cn.

EQUAL CONTRIBUTION

Y.Z., L.C., G.-Q.H., N.Z., X.-D.Z., K.-Y.Y., F.J., M.S., Y.-P.C., F.-Y.X., Y.S., J.M., and L.-L.T. contributed equally to this work.

PRIOR PRESENTATION

Presented at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31, 2019 (Best of ASCO).

SUPPORT

Supported by the Overseas Expertise Introduction Project for Discipline Innovation (111 Project, grant No. B14035), the Sun Yat-Sen University Clinical Research 5010 Program (grant number 2014009), the National Natural Science Foundation of China (81930072 and 82172870), the Natural Science Foundation of Guangdong Province (2017A030312003), and the Key-Area Research and Development Program of Guangdong Province (2019B020230002).

CLINICAL TRIAL INFORMATION

NCT01872962

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/jco.22.00327.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/jco.22.00327.

AUTHOR CONTRIBUTIONS

Conception and design: Yuan Zhang, Lei Chen, Ying Sun, Jun Ma, Ling-Long Tang
Financial support: Jun Ma
Administrative support: Jun Ma
Provision of study materials or patients: Ning Zhang, Xiao-Dong Zhu, Kun-Yu Yang, Jin-Hua Long, Fang-Yun Xie, Jun Ma
Collection and assembly of data: Yuan Zhang, Guo-Qing Hu, Ning Zhang, Kun-Yu Yang, Feng Jin, Mei Shi, Wei-Han Hu, Zhi-Bin Cheng, Si-Yang Wang, Ye Tian, Xi-Cheng Wang, Yan Sun, Jin-Gao Li, Wen-Fei Li, Yu-Hong Li, Yan-Ping Mao, Guan-Qun Zhou, Rui Sun, Xu Liu, Guo-Xian Long, Shao-Qiang Liang, Ling Li, Jing Huang, Jin-Hua Long, Jian Zang, Qiao-Dan Liu, Li Zou, Qiong-Fei Su, Bao-Min Zheng, Yun Xiao, Fei Han, Hao-Yuan Mo, Xiao-Jing Du, Cheng Xu, Na Liu, Ying-Qin Li, Fang-Yun Xie, Jun Ma, Ling-Long Tang
Data analysis and interpretation: Yuan Zhang, Xiao-Dong Zhu, Yu-Pei Chen, Xu Liu, Rui Guo, Ying Guo, Jia-Wei Lv, Cheng Xu, Jun Ma, Ling-Long Tang
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

This was an investigator-initiated study. Qilu Pharmaceutical provided free drugs (gemcitabine and cisplatin) for this study. We thank the research, nursing, and medical staff at each contributing center. We also thank the participating patients and their families. We extend gratitude to Hui-Xia Feng, Ying Wang, Rui-Yao Ou, and Juan Liu (Sun Yat-sen University Cancer Center) for their help assistance with logistic support and data management. We thank Melvin Chua (National Cancer Centre Singapore) for his assistance with trial design, data interpretation, and critical revision of the manuscript. We are grateful to the National Clinical Study Center for Anticancer Drugs, Sun Yat-sen University Cancer Center, for the statistical analyses, data management, and trial monitoring.

REFERENCES

1. Pathmanathan R, Prasad U, Sadler R, et al: Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. N Engl J Med 333:693-698, 1995
2. Mao YP, Xie FY, Liu LZ, et al: Re-evaluation of 6th edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement based on magnetic resonance imaging. Int J Radiat Oncol Biol Phys 73:1326-1334, 2009
3. Zhang Y, Chen L, Hu GQ, et al: Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. N Engl J Med 381:1124-1135, 2019

4. Edge SB, Byrd DR, Compton CC, et al: AJCC Cancer Staging Manual (ed 7). New York, NY, Springer, 2010, pp 7
5. Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341-1346, 1995
6. Pocock SJ, Clayton TC, Altman DG: Survival plots of time-to-event outcomes in clinical trials: Good practice and pitfalls. Lancet 359:1686-1689, 2002
7. Schoenfeld D: Partial residuals for the proportional hazards regression model. Biometrika 69:239-241, 1982
8. Luo WJ, Zou WQ, Liang SB, et al: Combining tumor response and personalized risk assessment: Potential for adaptation of concurrent chemotherapy in locoregionally advanced nasopharyngeal carcinoma in the intensity-modulated radiotherapy era. Radiother Oncol 155:56-64, 2020
9. Le QT, Colevas AD, O'Sullivan B, et al: Current treatment landscape of nasopharyngeal carcinoma and potential trials evaluating the value of immunotherapy. J Natl Cancer Inst 111:655-663, 2019
10. Mai HQ, Chen QY, Chen D, et al: Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: A multicenter randomized phase 3 trial. Nat Med 27:1536-1543, 2021
11. Yang Y, Qu S, Li J, et al: Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): A multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 22:1162-1174, 2021
12. Chen YP, Liu X, Zhou Q, et al: Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: A multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. Lancet 398:303-313, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Final Overall Survival Analysis of Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma: A Multicenter, Randomized Phase III Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jun Ma
Research Funding: Bristol Myers Squibb Foundation, Varian Medical Systems

No other potential conflicts of interest were reported.