Gemcitabine Plus Cisplatin Versus Fluorouracil Plus Cisplatin as First-Line Therapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: Final Overall Survival Analysis of GEM20110714 Phase III Study

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abstract

PURPOSE GEM 20110714 (ClinicalTrials.gov identifier: NCT01528618), the first randomized, phase III study of systemic chemotherapy in recurrent or metastatic nasopharyngeal carcinoma (NPC), reported significant progression-free survival improvement with gemcitabine plus cisplatin (GP) versus fluorouracil plus cisplatin (FP; hazard ratio, 0.55; 95% CI, 0.44 to 0.68; P < .001). Data from the final analysis of overall survival (OS) are presented here.

METHODS From February 2012 to October 2015, 362 patients were randomly assigned to receive either GP (gemcitabine 1 g/m² once daily on days 1 and 8 and cisplatin 80 mg/m² once daily on day 1; n = 181) or FP (fluorouracil 4 g/m² in continuous intravenous infusion over 96 hours and cisplatin 80 mg/m² once daily on day 1; n = 181) once every 21 days. The primary end point was progression-free survival, which has been previously reported; OS was a secondary end point.

RESULTS After a median follow-up time of 69.5 months with GP and 69.7 months with FP, 148 (81.8%) and 166 (91.7%) deaths occurred in the GP and FP arms, respectively. The estimated hazard ratio for OS was 0.72 (95% CI, 0.58 to 0.90; two-sided P = .004). The median OS was 22.1 months (95% CI, 19.2 to 25.0 months) with GP versus 18.6 months (95% CI, 15.4 to 21.7 months) with FP. The OS probabilities at 1, 3, and 5 years were 79.9% versus 71.8%, 31.0% versus 20.4%, and 19.2% versus 7.8%, respectively. Poststudy therapy was administered in 51.9% and 55.2% of patients in the GP and FP arms, respectively.

CONCLUSION Among patients with previously untreated advanced nasopharyngeal carcinoma, those who receive GP have longer OS than those receive FP. Gemcitabine plus cisplatin should be considered a preferred front-line option for these patients.
Recently, a phase III study demonstrated that induction chemotherapy with GP followed by concurrent chemoradiotherapy significantly prolonged disease-free survival in NPC. However, there is a paucity of information on whether long-term survival benefit could be obtained from GP regimen in NPC. Here, we report the results of the final OS analysis from the GEM20110714 trial.

**METHODS**

Full details of the multicenter, randomized, open-label, phase III GEM20110714 study (ClinicalTrials.gov identifier: NCT01528618) have been published previously. The Protocol (online only) was approved by site-specific ethics review boards. Study conduct was guided by principles of good clinical practice and the Declaration of Helsinki. Patients provided written informed consent before enrollment.

**Patients**

Eligible patients had confirmed, newly diagnosed stage IV, or recurrent NPC not suitable for local treatment. In brief, RM-NPC patients who were age older than 18 years, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and had at least one measurable lesion per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) were enrolled in the study. Overall, 362 patients were enrolled from 22 sites and randomly assigned (1:1) via an interactive phone response system to receive GP or FP from February 2012 to October 2015. Random assignment was centrally conducted and mediated by an independent contract research organization (H&J, Beijing, China) and was not stratified.

**Treatments**

Patients received either GP (gemcitabine 1 g/m² given intravenously [IV] once daily on days 1 and 8 and cisplatin 80 mg/m² IV once daily on day 1) or FP (fluorouracil 4 g/m² given via continuous intravenous infusion over 96 hours starting from day 1 and cisplatin 80 mg/m² once daily IV on day 1) once every 21 days for a maximum of six cycles, or until disease progression, death, intolerable toxicities, or patient-physician decision. Precautionary premedication regimens were undertaken with cisplatin treatment (antiemetic, diuretic, and hydration treatment). No more than two dose modifications as specified by the protocol were permitted.

**Assessment**

Tumor response was evaluated by imaging according to RECIST 1.1 by the independent image committee every two cycles until disease progression. Postprogression survival status and subsequent anticancer therapy was obtained every 3 months. The primary end point was PFS. OS was a secondary end point. Briefly, PFS was defined as the time from random assignment until objective tumor progression (independent image committee assessment) or death (any cause). OS was defined as the time from random assignment until death (any cause) or censored at the last date of known survival. Detection of Epstein-Barr virus (EBV) DNA was optional, depending on the laboratory availability of the participating centers. All adverse events were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Full data of adverse events have been reported previously.

**Statistical Analyses**

All patients randomly assigned were eligible for efficacy analyses (intent-to-treat). Sample size estimations have been published previously and were to detect a 50% improvement in PFS, with no hierarchy analysis assigned to OS based on the statistical analysis plan. The final OS and the updated PFS were conducted on the intent-to-treat population, with minimum follow-up of 5 years and despite the maturity of OS. OS was analyzed by using the unadjusted Cox proportional hazards regression model to estimate HRs and 95% CIs. Kaplan-Meier curves were used to estimate median survival and survival probabilities at 1, 3, and 5 years. Differences in survival were assessed by using a two-sided log-rank test. The restricted mean survival time
(RMST) and 95% CIs were estimated to supplement the OS analysis. The RMST was restricted at 88.73 months, representing the last follow-up time point of the patients in the FP group at data cutoff. Exploratory analyses assessing the multivariable prognostic significance of baseline factors were also carried out.

All tests were two-sided with a nominal type I error (α) of 5%. Significance levels (P values) were not adjusted for multiplicity. All analyses were performed using SPSS, version 25.0 (Chicago, IL), except the RMST analysis, comparison of median OS, and comparison of 1-, 3-, and 5-year survival rates, which were completed using the R program, version 3.4.3, with the package surv2sampleComp.8

RESULTS

Patients and Study Treatment

A total of 362 patients were randomly assigned to receive GP (n = 181) or FP (n = 181). Patient disposition is summarized in Figure 1. Baseline demographics and disease characteristics were generally well balanced between the treatment groups (Table 1). Final date of study treatment was October 20, 2016.

Final OS Analysis

As of December 17, 2020, duration of follow-up was comparable between arms: 69.5 months (95% CI, 63.3 to 75.6) with GP and 69.7 months (95% CI, 56.4 to 83.0) with FP. A total of 314 deaths (86.7%) had occurred: 148 (81.8%) of 181 patients in the GP arm and 166 (91.7%) of 181 patients in the FP arm. OS was significantly longer with GP than with FP (HR, 0.72; 95% CI, 0.58 to 0.90; two-sided P = .004); the median OS was 22.1 months (95% CI, 20.9 to 23.3) with GP versus 18.6 months (95% CI, 15.4 to 21.7) with FP (Fig 2A). The difference of median OS between the GP arm and the FP arm was 3.53 months (95% CI, 2.09 to 5.07; P = .123). The OS probabilities at 1, 3, and 5 years for the GP arm versus the FP arm were 79.9% (95% CI, 73.3 to 85.1) versus 71.8% (95% CI, 64.7 to 77.8), 31.0% (95% CI, 24.3 to 37.9) versus 20.4% (95% CI, 14.9 to 26.6), and 19.2% (95% CI, 13.6 to 25.5) versus 7.8% (95% CI, 4.3 to 12.6), with P values of .093, .021, and < .001, respectively. The RMST for OS was 33.0 months.

FIG 1. CONSORT diagram of patient disposition.
TABLE 1. Baseline Characteristics of the Intention-to-Treat Population

| Characteristics                          | GP (n = 181) | FP (n = 181) |
|-----------------------------------------|--------------|--------------|
| Sex                                      |              |              |
| Male                                     | 141 (77.9)   | 153 (84.5)   |
| Female                                   | 40 (22.1)    | 28 (15.5)    |
| ECOG PS                                  |              |              |
| 0                                        | 59 (32.6)    | 62 (34.3)    |
| 1                                        | 122 (67.4)   | 119 (65.7)   |
| Age, median, years (ranges)              | 47 (19-78)   | 47 (21-73)   |
| ≤ 50                                     | 116 (64.1)   | 110 (60.8)   |
| > 50                                     | 65 (35.9)    | 71 (39.2)    |
| Smoking status                           |              |              |
| Ever or current smokers                  | 40 (22.1)    | 53 (29.3)    |
| Nonsmokers                               | 141 (77.9)   | 128 (70.7)   |
| Histologya                               |              |              |
| Nonkeratinizing undifferentiated (type III) | 150 (82.9)   | 150 (82.9)   |
| Nonkeratinizing differentiated (type II)  | 18 (9.9)     | 13 (7.2)     |
| Keratinizing (type I)                    | 5 (2.8)      | 4 (2.2)      |
| Others                                   | 8 (4.4)      | 14 (7.7)     |
| Stage                                    |              |              |
| De novo metastases                       | 45 (24.9)    | 59 (32.6)    |
| Recurrentb                               | 136 (75.1)   | 122 (67.4)   |
| Metastatic organs at screening           |              |              |
| Lung                                     | 82 (45.3)    | 81 (44.8)    |
| Liver                                    | 67 (37.0)    | 76 (42.0)    |
| Bone                                     | 54 (29.8)    | 55 (30.4)    |
| Others                                   | 11 (6.1)     | 10 (5.5)     |
| No. of metastatic organs                 |              |              |
| 1                                        | 96 (53.0)    | 94 (51.9)    |
| 2                                        | 49 (27.1)    | 56 (30.9)    |
| ≥ 3                                      | 36 (19.9)    | 31 (17.1)    |
| Previous chemotherapy                    |              |              |
| Induction                                | 75 (41.4)    | 60 (33.1)    |
| Concurrent                               | 67 (37.0)    | 62 (34.3)    |
| Adjuvant                                 | 21 (11.6)    | 19 (10.5)    |
| None                                     | 67 (37.0)    | 78 (43.1)    |
| Previous chemotherapeutic agents         |              |              |
| Platinum                                 | 106 (58.6)   | 91 (50.3)    |
| Fluorouracil                             | 55 (30.4)    | 43 (23.8)    |
| Docetaxel                                | 19 (10.5)    | 11 (6.1)     |
| Paclitaxel                               | 31 (17.1)    | 30 (16.6)    |

NOTE. Data are presented as No. (%) unless otherwise noted. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FP, fluorouracil plus cisplatin; GP, gemcitabine plus cisplatin. Histology was categorized according to the WHO Classification of Tumors. Development of locoregional recurrence or distant metastasis after radical radiotherapy not amenable for local therapy.

(95% CI, 29.3 to 37.2) in the GP group and 25.4 months (95% CI, 22.4 to 28.6) in the FP group (P = .003).

Although the study was not designed to have sufficient power to test interaction, subgroup OS analyses were generally consistent with the primary analysis of OS except in patients with de novo metastasis and subgroup of bone metastasis (Fig 3). The Kaplan-Meier estimates for the subgroup comparison between patients with de novo metastasis and recurrence and between bone metastasis status are provided in the Data Supplement (online only).

Poststudy Treatment

In total, 94 patients (51.9%) in the GP group and 100 (55.2%) in the FP group started a first subsequent systemic therapy after discontinuation of study treatment (Table 2). Among them, 64 of 94 (68.1%) in the GP group and 83 of 100 (83.0%) in the FP group received platinum-based combination chemotherapy. The most common non-platinum agent in first subsequent therapy was taxanes. Overall response rate (ORR) was 20.2% (19 out of 94) in patients who received first subsequent treatment in the GP arm; 44.7% (42 out of 94) and 23.4% (22 out of 94) of these patients reported stable disease (SD) and progressive disease (PD), respectively. For patients in the FP arm who received first subsequent therapy, partial response (PR) was reported in 17.0% (17 out of 100), SD in 52.0% (52 out of 100), and PD in 20% (20 out of 100). When the data for survival were censored at the time of the initiation of second-line therapy, there was significantly longer OS with GP than with FP (median OS, 29.3 v 16.1 months; HR, 0.51; 95% CI, 0.36 to 0.71; P < .001).

Among the patients who received a first subsequent therapy, the number of those who received a second subsequent therapy was 35 of 94 (37.2%) in the GP arm and 47 of 100 (47.0%) in the FP arm. Forty-two (23.2%) of 181 patients assigned to GP had poststudy treatment with fluorouracil, capecitabine, tegafur, or S-1; whereas in the FP arm, 47 (26.0%) of 181 patients received gemcitabine after discontinuation of study treatment. A total of 10 patients in the GP arm and 10 patients in the FP arm received ICIs. Among them, 6 (30.0%) had PR, 6 (30.0%) had SD, and 8 (40.0%) had PD.

5-Year Survivors

Among the 25 patients who survived ≥ 5 years in the GP arm, four (16.0%) had not progressed by 5 years and 15 (60.0%) had progressed, and six (24.0%) had been censored for PFS (Data Supplement). Among the 10 5-year survivors in the FP arm, nine (90.0%) had progressed and one (10.0%) was censored for PFS at 11.5 months (Data Supplement).

Among the 5-year survivors, EBV titer was available from 21 and eight patients in the GP arm and FP arm, respectively. Eight of the 21 (38.1%) patients in the GP arm have
undetectable baseline EBV DNA, whereas EBV DNA level in the remaining 13 (61.9%) patients rapidly dropped to zero after study treatment. For the eight patients in the FP arm, one (12.5%) had undetectable baseline EBV level and six (75.0%) had elevated baseline EBV DNA but become undetectable after study treatment.

Four of 25 GP-treated patients who survived 5 years had ever received ICIs and two had durable response for over 2 years. Among 10 patients who survived 5 years in the FP arm, four had received ICIs and two of them had PR that lasted for over 2 years.

Multivariable Analysis for OS

A univariable Cox regression model was used to estimate the effect on OS of selected baseline characteristics (Data Supplement). In univariable analysis, the following variables were significantly associated with OS: sex, smoking status, ECOG PS, number of metastatic sites, liver metastasis, bone metastasis, and baseline EBV DNA. Multivariate analysis (Data Supplement) showed a better survival in patients who were randomly assigned to the GP group (P = .008), had better ECOG PS (P < .001), without liver metastasis (P = .05), and had low baseline EBV load (all with P < .05).

Updated PFS

PFS rates consistently favored GP versus FP over time and consistent with previous report (Fig 2B), with similar risk of disease progression or death (HR, 0.54; 95% CI, 0.43 to 0.67). The PFS probabilities at 1, 3, and 5 years were 21.2% (15.5 to 27.6) versus 6.0% (95% CI, 3.1 to 10.3), 8.5% (95% CI, 4.6 to 13.9) versus 1.1% (95% CI, 0.1 to 4.8), and 7.6% (95% CI, 3.9 to 12.9) versus 0% in the GP versus FP arms, respectively, all with P values of < .001.

DISCUSSION

The GEM20110714 study established the role of first-line GP for patients with RM-NPC. Here, we report the final OS results after an additional 4 years of follow-up, which, to date, is the longest duration of follow-up in RM-NPC. The results show that the GP regimen produces an OS benefit for these patients, with a 28% reduction in the risk of death and an improvement of almost 4 months in median OS. Particularly, the survival curves separated early. This is the first phase III trial to demonstrate a significant OS benefit for palliative systemic chemotherapy in NPC. The median OS was 22.1 months for the GP group and 18.6 months for the FP group, which was similar to that reported in a real-world study of cisplatin-based chemotherapy in RM-NPC. However, a few retrospective studies or clinical trials reported longer or shorter median survival than that observed in our study. Possible explanations may include the proportion of patients with subsequent therapies (ie, only about half of the patients had poststudy treatment in our study), differences in patients’ characteristics, maturity of survival data, and different period of patient recruitment. The survival results in this report were unlikely confounded by poststudy therapy, given the similar rate of poststudy treatment for GP versus FP (51.9% v 55.2%) and the relatively balanced selection of therapies between both groups.
| Subgroups                  | GP Patients | Median OS (months) | FP Patients | Median OS (months) | HR (95% CI) | P     |
|---------------------------|-------------|--------------------|-------------|--------------------|-------------|-------|
| All patients              | 181         | 22.1               | 181         | 18.6               | 0.72 (0.58 to 0.90) | .004  |
| Age, years                |             |                    |             |                    |             |       |
| ≤ 50                      | 116         | 23.7               | 110         | 18.3               | 0.68 (0.51 to 0.91) | .008  |
| > 50                      | 65          | 20.7               | 71          | 18.6               | 0.81 (0.57 to 1.17) | .264  |
| Sex                       |             |                    |             |                    |             |       |
| Male                      | 141         | 22.1               | 153         | 18.3               | 0.72 (0.56 to 0.92) | .008  |
| Female                    | 40          | 21.5               | 28          | 20.8               | 0.81 (0.47 to 1.40) | .450  |
| Smoking status            |             |                    |             |                    |             |       |
| Nonsmoker                 | 141         | 21.9               | 128         | 18.7               | 0.71 (0.55 to 0.93) | .012  |
| Current or ever smoker    | 40          | 22.1               | 53          | 18.3               | 0.78 (0.51 to 1.20) | .253  |
| Histology                 |             |                    |             |                    |             |       |
| Type II                   | 18          | 24.5               | 13          | 13.5               | 0.64 (0.30 to 1.37) | .252  |
| Type III                  | 181         | 22.1               | 150         | 18.7               | 0.72 (0.56 to 0.92) | .008  |
| Others                    | 13          | 19.5               | 18          | 18.3               | 0.81 (0.37 to 1.79) | .603  |
| Stage                     |             |                    |             |                    |             |       |
| De novo metastasis        | 45          | 19.0               | 59          | 21.5               | 1.01 (0.66 to 1.54) | .977  |
| Recurrent                 | 136         | 24.0               | 122         | 17.0               | 0.63 (0.48 to 0.82) | .001  |
| ECOG PS                   |             |                    |             |                    |             |       |
| 0                         | 59          | 31.5               | 62          | 25.6               | 0.59 (0.40 to 0.88) | .010  |
| 1                         | 122         | 19.5               | 119         | 15.6               | 0.78 (0.59 to 1.01) | .063  |
| No. of metastasis         |             |                    |             |                    |             |       |
| Oligo                     | 96          | 25.7               | 94          | 21.5               | 0.63 (0.46 to 0.86) | .003  |
| Multiple                  | 85          | 17.9               | 87          | 16.5               | 0.86 (0.62 to 1.18) | .349  |
| Lung metastasis           |             |                    |             |                    |             |       |
| No                        | 99          | 21.5               | 100         | 17.0               | 0.72 (0.53 to 0.98) | .039  |
| Yes                       | 82          | 23.1               | 81          | 20.8               | 0.74 (0.54 to 1.01) | .061  |
| Liver metastasis          |             |                    |             |                    |             |       |
| No                        | 114         | 24.5               | 102         | 23.4               | 0.78 (0.58 to 1.05) | .105  |
| Yes                       | 67          | 19.5               | 76          | 14.4               | 0.65 (0.46 to 0.91) | .012  |
| Bone metastasis           |             |                    |             |                    |             |       |
| No                        | 127         | 25.1               | 126         | 20.8               | 0.64 (0.49 to 0.84) | .001  |
| Yes                       | 54          | 15.6               | 55          | 15.8               | 0.91 (0.61 to 1.34) | .620  |
| No. of chemotherapy       |             |                    |             |                    |             |       |
| ≤ 4                       | 60          | 14.6               | 79          | 14.9               | 0.78 (0.55 to 1.12) | .181  |
| 5                         | 16          | 14.4               | 11          | 18.3               | 0.82 (0.36 to 1.89) | .647  |
| 6                         | 105         | 24.9               | 91          | 23.8               | 0.73 (0.54 to 1.00) | .047  |

**FIG 3.** OS HRs (GP over FP) in subgroups according to baseline characteristics. ECOG PS, Eastern Cooperative Oncology Group performance status; FP, fluorouracil plus cisplatin; GP, gemcitabine plus cisplatin; HR, hazard ratio; OS, overall survival; No. of chemotherapy, cycles of chemotherapy for the treatment groups.
arms. Response to the first subsequent systemic therapy was also comparable between GP and FP arms (20.2% vs 17.0%). Moreover, the proportion of patients in the FP arm who crossed over to gemcitabine was similar to that of patients who crossed to fluorouracil (or its analogs) in the GP arm (26.0% vs 23.2%). A sensitivity analysis of survival indicated that the survival difference was not attributed to the use of subsequent therapy. Therefore, the between-group survival difference was mainly driven by the first-line PFS. Noteworthy, only about a quarter of patients received subsequent treatment with gemcitabine in the FP group. This may be another reason for the OS decrement in the FP group and highlights the importance of placing gemcitabine in the front-line setting.

The 5-year timepoint is a landmark to evaluate long-term survival. In this report, more patients survived ≥ 5 years in GP versus FP arms (13.8% vs 5.5%), and the 5-year OS rate estimate also favors GP group (19.2% vs 7.8%). There seems a survival plateau starting from 5 years in both groups, suggesting that survival beyond 5 years may also be possible in RM-NPC. Despite the descriptive nature, several potential characteristics might be related to 5-year survival; these include negative baseline EBV DNA or early EBV clearance, which also has been documented in several retrospective studies. Another possible contributor to long-term survival was immunotherapy. Among the 5-year survivors, four had ≥ 2 years’ durations of response to ICIs. Several studies also showed promising activities of anti-programmed death-1 (PD-1) monotherapy for RM-NPC, with reported ORRs ranging from 20.5% to 34.1%. In this study, the antitumor activity of ICIs (ORR, 30.0%) was similar to that reported in the above-mentioned trials. However, the role of ICIs in salvage treatment in RM-NPC needs to be tested in randomized trials. The phase III KEYNOTE-122 study is ongoing to compare pembrolizumab with chemotherapy as second-line treatment of RM-NPC (NCT02611960). In preliminary results from a randomized phase II trial, spartalizumab (PDR001) had an ORR of 17%, but did not improve PFS compared with chemotherapy for platinum-refractory NPC.

Almost all subgroups demonstrated positive survival results, demonstrating the potential for GP to improve outcomes in a diverse patient population. However, HRs were close to 1.00 among patients with de novo metastasis, who have distinct disease features and clinical outcomes compared those with recurrent disease. Recently, a phase III study demonstrated that FP chemotherapy plus radiotherapy significantly improved OS compared with FP alone in patients with de novo metastatic NPC (HR, 0.36). However, future work is needed to address the optimal treatment modality for this patient group in whom the standard of care has become GP.

### TABLE 2. Poststudy Treatment After Progression on Study

| Treatment | GP (n = 181) | FP (n = 181) |
|-----------|--------------|--------------|
|           | First Subsequent Treatment | Second or Greater Subsequent Treatment(s) | First Subsequent Treatment | Second or Greater Subsequent Treatment(s) |
| No. of patients (%) | 94 (51.9) | 35 (19.3) | 100 (55.2) | 47 (26.0) |
| Chemotherapy | | | | |
| Platinum | 64 (35.4) | 12 (6.6) | 83 (45.9) | 19 (10.5) |
| Paclitaxel | 43 (23.8) | 4 (2.2) | 54 (29.8) | 11 (6.1) |
| Docetaxel | 12 (6.6) | 5 (2.8) | 4 (2.2) | 6 (3.3) |
| Nab-paclitaxel | 11 (6.1) | 0 | 10 (5.5) | 1 (0.6) |
| Gemcitabine | 2 (1.1) | 8 (4.4) | 21 (11.6) | 30 (16.6) |
| Fluorouracil | 10 (5.5) | 8 (4.4) | 2 (1.1) | 3 (1.7) |
| Capecitabine | 8 (4.4) | 14 (7.7) | 6 (3.3) | 16 (8.8) |
| Tegafur | 2 (1.1) | 0 | 3 (1.7) | 2 (1.1) |
| S-1 | 5 (2.8) | 5 (2.8) | 0 | 2 (1.1) |
| Nonchemotherapy | | | | |
| PD-1 or PD-L1 inhibitor | 3 (1.7) | 5 (2.8) | 0 | 10 (5.5) |
| CTLA-4 inhibitor | 3 (1.7) | 1 (0.6) | 0 | 1 (0.6) |
| Anti-EGFR antibody | 2 (1.1) | 0 | 2 (1.1) | 1 (0.6) |
| Other | 3 (1.7) | 13 (7.2) | 0 | 19 (10.5) |

NOTE. Data are presented as No. (%).

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; EGFR, epidermal growth factor receptor; FP, fluorouracil plus cisplatin; GP, gemcitabine plus cisplatin; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.
In the two treatment groups, approximately 50% of the patients discontinued the trial drug and did not receive a subsequent therapy, owing to death in substantial patients. This observation becomes the basis for using the most effective therapies in the upfront treatment. Several previous studies have shown that gemcitabine-based therapy is effective in NPC.\textsuperscript{10,12,24-26} A phase III trial showed that induction chemotherapy with GP significantly improved disease-free survival in locally advanced NPC.\textsuperscript{6} However, this study did not provide poststudy treatment information for patients who had recurrent or metastatic disease after chemoradiotherapy. In our study, only one patient had previous induction therapy with GP. Therefore, it remains unknown whether GP remains effective in patients who relapse after induction chemotherapy with GP regimen followed by radical chemoradiotherapy. Since GP has become the standard-of-care treatment for NPC, accumulating studies are ongoing to assess the added value of novel agents to GP regimen. These include an anti–PD-1 antibody (NCT03707509, NCT04458909, NCT03924986, NCT03581786) or an angiogenesis agent (NCT03601975, NCT01915134). Full safety and efficacy data from these studies are yet to be reported but preliminary data from a phase I study showed that camrelizumab plus GP has promising antitumor activity in RM-NPC.\textsuperscript{17} In the 2021 ASCO annual meeting, two phase III trials reported the primary PFS results of GP plus a PD-1 inhibitor versus GP plus placebo in RM-NPC. In the CAPTAIN-1st study, median PFS was 10.8 months for GP plus camrelizumab and 6.9 months for GP plus placebo (HR, 0.51; one-sided $P < .0001$).\textsuperscript{27} In the JUPITER-02 study, a significant improvement in PFS was detected for GP plus toripalimab compared with GP plus placebo (median, 11.7 months vs 8.0 months; HR, 0.52; $P = .003$).\textsuperscript{28} OS data from both studies were not mature yet (for example, only 20.8% of the patients in the JUPITER-02 study died). Considering that PD-1 inhibitors are effective in subsequent treatment, long-term follow-up will be required for these studies because OS should be a more relevant end point than PFS is. Another issue that remains to be addressed is whether cisplatin could be replaced by other platinum. In nonmetastatic NPC, nedaplatin and lobaplatin are noninferior to cisplatin in terms of efficacy.\textsuperscript{29-30} Several phase II studies also indicate that carboplatin is effective in RM-NPC.\textsuperscript{31-34} Our study also identified several independent prognostic factors for RM-NPC, including liver metastasis, ECOG PS, and EBV load. This finding is also reported in some retrospective studies.\textsuperscript{9,15} indicating that these prognostic factors should be considered as stratification factors in future randomized study design.

One limitation of this report is that no hierarchy analysis was assigned to OS. A little caution should be exercised when interpreting the OS results. This limitation aside, the final analysis of the GEM20110714 study provides a new benchmark for OS in patients with RM-NPC and highlights the benefit of first-line treatment with GP for prolonging survival in this patient population.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Gemcitabine Plus Cisplatin Versus Fluorouracil Plus Cisplatin as First-Line Therapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: Final Overall Survival Analysis of GEM20110714 Phase III Study

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