A randomized, multicenter phase III clinical trial comparing gemcitabine plus cisplatin with 5-FU plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma (NPC)

(FULL PROTOCOL)

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1. PROTOCOL SUMMARY

This a randomized, open-label, multicenter phase III study that compare the efficacy and safety of Gemcitabine (Gemzar, Lilly) plus cisplatin (GP) with 5-FU plus cisplatin (FP) as first-line treatment in recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC). The study population consists of chemotherapy naïve metastatic nasopharyngeal carcinoma (NPC) patients (stage IVC) or recurrent NPC patients that have failed the radical radiotherapy. The primary objective of the study is to demonstrate that GP is superior to FP, in prolonging progression-free survival in patients with recurrent or metastatic NPC, as assessed by blinded independent radiologists. Secondary objectives are to compare clinical efficacy including objective response rate (ORR) and disease control rate (DCR); to explore the difference of overall survival (OS) between the two groups; and to assess the safety and tolerability of GP and FP regimens. Treatment efficacy will be evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Adverse events were assessed according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (NCI-CTCAE).

2. INTRODUCTION

2.1. Background
Nasopharyngeal carcinoma (NPC) is one of the most common cancers in south China and south-east Asia [1]. NPC is a radio- and chemo-sensitive tumor, and radiotherapy is considered to be the primary treatment for most cases. The 5-year survival rate (all stages) is around 50% [2]. In other words, more than half of the NPC cases will eventually fail radiotherapy and reasons of the failure are mainly distant metastasis.

More than 95% of NPC are undifferentiated or poorly differentiated keratinized carcinoma [3]. NPC is more responsive to chemotherapy than other head and neck cancers. For recurrent/metastatic (R/M) NPC, platinum-containing regimens are regarded as the standard first-line treatment for R/M NPC [4]. However, there are no randomized trials that have defined the optimal regimens. Currently, the cisplatin and continuous intravenous infusion (civ) 5-Fu (FP) is widely used in metastatic NPC patients for many years with the response rate of 40%-65% [5-8]. However, the response period is usually short and the adverse reaction is frequent and badly tolerant. What’s more, the catheters and pumps are necessary for continuous infusion of 5-Fu, which add to the cost, hospital stay, immobility and inconvenience of the treatment. Therefore, finding new combination chemotherapies to extend survival in R/M NPC patients with acceptable toxicity is of the utmost importance.

2.2. Rationale

Gemcitabine (Gemzar, Lilly) is a nucleoside analog with broad...
anti-solid tumor activity, which inhibits DNA synthesis. Its activity against tumor has been documented in pancreatic cancer, breast cancer and non-small cell lung cancer [9]. Recently several clinical trials have demonstrated that gemcitabine is effective in the treatment of advanced NPC and achieved an impressive survival outcome. Preclinical and clinical data show the synergistic activity between gemcitabine and cisplatin without overlapping toxicity. These small trials call for the potentiality that the GP regimen comes to the standard first line choice instead of the PF regimen.

In 2002, two studies reported that gemcitabine was an active and well tolerable drug for patients with NPC. Foo KF conducted two parallel phase II trials [10] in chemo-naive and previously treated patients with metastatic NPC to evaluate the tumor response, progression-free and overall survival, and toxicity of gemcitabine. They found the overall response rate was 28% for the chemo naive patients and 48% for previously treated patients, for another, they found the toxicity of gemcitabine in the treatment of NPC is minimal. Later, M BB confirmed that Gemcitabine is an active and tolerable drug for patients with NPC [11].

In 2005, a pilot study was performed to evaluate the efficacy and safety of gemcitabine and cisplatin combination in the treatment of patients with NPC [12]. In the study, fourteen patients were assessable for
response and 92.9% achieved an overall response with 21.4% complete response. In another study[13] aiming to evaluate the efficacy and toxicity of gemcitabine plus cisplatin (GP) chemotherapy in patients with R/M NPC, Jialei Wang et al. found that Of the 75 evaluable patients, 4 achieved CR and 28 patients achieved PR, accounting for an overall response rate of 42.7%. The 1-year survival rate was 33.9%, and median progression-free survival and overall survival were 5.6 and 9.0 months, respectively. Grade 3 and 4 toxicities were uncommon. These studies strongly indicated that the GP chemotherapy regimen has a promising effectiveness and well tolerated side effects in the treatment of R/M NPC.

Besides, the GP chemotherapy regimen was also proved effective in the induction chemotherapy [14, 15]. Chua DT and Yau TK found that the combination cisplatin and gemcitabine is active and well tolerated in locally recurrent NPC and patients with stage IV (A-B) NPC. The combination with other agents has also been proved active in the treatment of NPC. A phase II study of gemcitabine plus vinorelbine [16] indicated that the GN regimen is a reasonable choice for patients with cisplatin-resistant NPC. Several other agents have also been found effective when combined with gemcitabine [17-19], such as paclitaxel, carboplatin, oxaplatin and so on.

In our previously phase II study [20], we found that the overall response rate of single agent gemcitabine was 43.8% in the 32 assessable
patients with advanced NPC who has failed the platinum-based chemotherapy previously. The median time to progression was 5.1 months and median survival time was 16 months, 1 and 2 year survival rate was 67%, 12%, respectively. The effectiveness of gemcitabine was higher and side effects were minimal in advanced NPC patients after platinum-based chemotherapy failed. The results of this study was NCCN guideline lists the gemcitabine as one of the effective agents in advanced NPC [21].

However, the above-mentioned trials enrolled very limited number of patients. No high-level evidence was available to determine the standard first line regimen. Therefore, a randomized, multicenter phase III clinical trial is highly needed to further study the objective response and safety of GP regimen in the treatment of advanced NPC.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

Study Objectives:

Primary Objective:

- To demonstrate the superiority of gemcitabine plus cisplatin (GP) over 5-FU plus cisplatin (FP) in prolonging progression-free survival (PFS) in patients with recurrent and metastatic nasopharyngeal carcinoma.
Secondary Objectives:

- To compare the clinical efficacy including objective response rate (ORR) and disease control rate (DCR).
- To explore the survival difference of the patients in the two groups.
- To assess the safety and tolerability of these two regimens.

3.2. Endpoints

Primary Endpoints

- PFS based upon RECIST version 1.1 determined by independent radiology review.

Secondary Endpoints

- Overall survival (OS)
- ORR and DCR
- Any adverse events (AEs) and any laboratory abnormalities; their incidence, severity, seriousness.

4. STUDY DESIGN

This will be a randomized, multicenter phase III study. A total of 362 patients with recurrent or primary metastatic nasopharyngeal carcinoma will be randomized in a 1:1 ratio to receive GP regimen or PF regimen as first line chemotherapy regimen. No stratification factors were employed. Patients will receive treatment once every 3 weeks, for 4-6 cycles. This study will be carried out in multicenter.
Patients will continue the treatment until RECIST-defined progression of disease as determined by independent radiology review, unacceptable toxicity, death of any causes, or consent withdrawal. Patients who completed 4 to 6 cycles of chemotherapy and/or discontinue prior to RECIST-defined disease progression will continue on the study with per protocol tumor assessment until disease progression documented by independent radiology review or patients initiate other anti-cancer therapy, except for palliative local treatment to non-target lesions. Post-progression treatment is at the attending oncologists’ discretion.

5. PATIENT SELECTION

The patient population consists of recurrent or metastatic nasopharyngeal carcinoma patients who failed the radical radiotherapy or chemotherapy naïve metastatic patients.

5.1. Inclusion Criteria

Patient eligibility should be evaluated and documented by an appropriately qualified member of the investigator’s study team before patient inclusion. Patients must meet all of the following items to be eligible for enrolment.

1. Histologically or cytologically confirmed NPC

2. Primarily metastatic (or stage IVC as defined by the International Union against Cancer [UICC] and American Joint Committee on
Cancer [AJCC] staging system for NPC, seventh edition) or recurrent nasopharyngeal carcinoma unsuitable for local treatment.

3. Patients did not receive systemic chemotherapy for recurrent or metastatic disease, except for prior induction, concurrent, or adjuvant chemotherapy that was completed >6 months prior to randomization. Prior radical radiotherapy should also be >6 earlier than randomization.

4. Eastern Cooperative Oncology Group performance status of 0 or 1;

5. Age $\geq$ 18 years;

6. Adequate organ function as defined by the following criteria:

   - Bone Marrow function
     - White blood cell count of 4.0X10^9/L or more;
     - Absolute neutrophil of 2.0X10^9/L or more;
     - Haemoglobin concentrations of at least 90g/L;
     - Platelet count of 100X10^9/L or more;

   - Liver function:
     - Serum aspartate transaminase (AST) and alanine transaminase (ALT) less than 2.5 times of the upper limit of the normal (ULN) value; or AST and ALT less than 5 times if liver function abnormalities are due to underlying malignancy.
     - Total serum bilirubin less than 1.5 times ULN.
Renal function:

* Creatinine clearance rate (CCR) of more than 60ml/min. based on Cockcroft-Gault formulation:

\[\frac{(140 - \text{years of age}) \times \text{Weight (kg)}}{72 \times \text{serum Creatinine (mg/dL)}}\]

At least one measurable lesion according to RECIST 1.1 (Tumour lesions situated in a previously irradiated area are considered unmeasurable).

Amenable to regular follow-up;

Life expectancy over twelve weeks;

Signed and dated informed consent before the start of specific protocol procedures;

Ability to comply with trial requirements;

5.2. Exclusion Criteria

Patients presenting with any of the following items will not be included in the study:

1. Patients suitable for local treatment, except for palliative, limited-field radiation to non-target metastatic lesions; Induction, adjuvant or concurrent chemotherapy, chemoradiotherapy, or radiotherapy is permitted if at least 6 months has elapsed prior to study enrollment;

2. Active clinically serious infections (> grade 2 NCI-CTC AE version 3.0);
3. Serious infections (≥ grade 2 according to NCI-CTCAE, version 3.0);

4. Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment;

5. Central nervous system metastases;

6. Bone-only metastasis;

7. Life threatening medical conditions;

8. Previous or concurrent cancer that is distinct in primary site or histology from NPC EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors [Ta, Tis & T1] or any cancer curatively treated > 3 years prior to study entry.

5.3. Randomization

Patients will be randomized in a 1:1 ratio receive either GP or FP. Randomisation was done with a block size of six via a centralized interactive phone response system, with no stratification factors. Investigators in each study center assessed the eligibility of a patient. When the inclusion criteria were met, the patient’s assignment information would be sent to an outside Contract Research Organization (H&J, Beijing, China). The study coordinator sent the allocated treatment back to the investigators by phone.
6. STUDY TREATMENT

6.1. Allocation to Treatment

After a patient has provided written informed consent, has completed the necessary screening and been determined to be eligible for the study, the trial site should contact central randomization system for patient’s allocation of study treatment.

6.2. Drug Supplies

6.2.1. Gemcitabine

Gemcitabine (Gemzar) is kindly provided by Eli Lilly as single-use vials containing 200mg of Gemcitabine, which will be administered by intravenous infusion.

6.2.2. 5-FU

Commercially available Generic 5-FU will be supplied by study center and will be administered by continuous intravenous infusion.

6.2.3. Cisplatin

Commercially available Generic cisplatin will be supplied by the principle study center (Sun Yat-sen University Cancer Center), which will be delivered to each participating center. Cisplatin will be administered by infusion.

6.3. Administration

6.3.1. Gemcitabine plus cisplatin

Gemcitabine will be administered at a dose of 1,000 mg/m² by
intravenous infusion over 30 minutes on day 1 and day 8. Cisplatin will be administered at 80 mg/m² by intravenous infusion for 4 hours on day 1 after adequate hydration. Gemcitabine plus cisplatin will be repeated every 3 weeks for a maximum of 6 cycles unless patients refuse to continue study treatment, disease progression, death, or at the attending oncologists’ discretion.

6.3.2. 5-FU plus cisplatin

Before 5-FU administration, the patients are required to have peripherally inserted central catheter (PICC) insertion. X-ray is used to confirm that the catheter is at an appropriate spot. 5-FU will be given via continuous intravenous infusion at 4g/m² over 96 hours starting from day 1. Cisplatin will be administered at 80 mg/m² by intravenous infusion for 4 hours on day 1 after adequate hydration. 5-FU plus cisplatin will be repeated every 3 weeks for a maximum of 6 cycles unless patients refuse to continue study treatment, disease progression, death, or at the attending oncologists’ discretion.

6.4. Dose Modifications

Patients will be closely monitored for toxicity and any laboratory abnormalities. Each treatment group has its corresponding expected toxicities. Dosage adjustment is used based on the severity of toxic reaction. The toxicity grade is according to the NCI CTC AE 3.0 version. Doses may not be escalated once reduced. At most two dose
modifications of combination treatment are allowed.

6.4.1. Gemcitabine or 5-FU

In patients who had grade 3 or 4 haematological, grade 3 or 4 non-haematological, gemcitabine, 5-FU, and cisplatin treatments will be interrupted. If the toxic effects resolved to a grade lower than 2, the dose of gemcitabine or 5-FU will be restarted at 80% of the dose at the last appearance of the toxic effects. For neutropenia patients, day 8 gemcitabine could be given at a reduced dose or postponed for up to 5 days to allow recovery, otherwise it was discontinued (Table 1).

Table 1. Gemcitabine and 5-FU Dose modifications for grade 3 or 4 treatment-related hematological or non-hematological

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Drug</th>
<th>Initial dose mg/m2</th>
<th>Dose reduction (1st time) mg/m2</th>
<th>Dose reduction (2nd time) mg/m2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td>Gemcitabine</td>
<td>1000</td>
<td>800</td>
<td>640</td>
</tr>
<tr>
<td>PF</td>
<td>5-FU</td>
<td>1000*4d</td>
<td>800*4d</td>
<td>640*4d</td>
</tr>
</tbody>
</table>

6.4.2. Cisplatin

For cisplatin, dose modification was based upon pre-chemotherapy creatinine clearance rate (CCR) in every cycle calculated with Cockcroft formulation. If CCR was higher than or equal to 60 ml/min, cisplatin was given at full dose. If CCR was between 41 and 59 ml/min, equal dose to CCR value (mg/m2) was applied. If CCR was less than 41 ml/min, cisplatin was stopped in this cycle and the dose of cisplatin will be
evaluated in the next cycle (Table 2).

Table 2. Cisplatin Dose modifications for grade 3 or 4 treatment-related hematological or non-hematological

<table>
<thead>
<tr>
<th>CCR ≥ 60 ml/min</th>
<th>100% dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR 41-59 ml/min</td>
<td>Same as the CCR (ml/min) value.</td>
</tr>
<tr>
<td></td>
<td>(for example: if CCR is 45 ml/min, the dose of cisplatin is 45 mg/m2)</td>
</tr>
<tr>
<td>CCR ≤ 40 ml/min</td>
<td>Stop using cisplatin in this cycle. Adjust according to the CCR in the next cycle.</td>
</tr>
</tbody>
</table>

6.4.3. Re-treatment Criteria

Patients should not begin a new cycle with treatment unless:

- ANC is >1.5 x 10⁹ / L
- Platelet >75 x 10⁹ / L
- Calculated creatinine clearance rate is >40 ml/min
- Disappearance of mucosal inflammation and diarrhea

If these re-treatment criteria are not met on the day of a new treatment cycle is scheduled to start, GP or FP regimen may be delay for a maximum of 2 weeks. Day 8 gemcitabine should not be delayed for more than 5 days, otherwise it was discontinued at this cycle.

6.5. Special Toxicity Management

6.5.1. Nausea and/or vomiting

This study suggests that the combination of 5-HT3 receptor
antagonist and dexamethasone should be used before chemotherapy to prevent nausea. 5-HT3 receptor antagonist including: dolasetron, granisetron, ondansetron, palonosetron, tropisetron. According to previous studies, 5-HT3 receptor antagonists have similar efficacy and safety in the prevention of chemotherapy induced nausea and vomiting (CINV), which can be replaced each other. Corticosteroids can also prevent allergic reaction caused by chemotherapy drugs. If the patient is still nausea and vomiting after applying these preventive measures, other anti-nausea scheme might be attempted. No dose adjusting is needed if the patient has nausea and/or vomiting.

6.5.2. Allergic reaction (especially for gemcitabine and cisplatin)

Table 3. Allergic reactions and their management

<table>
<thead>
<tr>
<th>Mild symptoms: local skin reactions, such as itching, redness, rash</th>
<th>Bed guard and lower the infusion rate until the symptoms recover, and then, use the original plan to complete infusion. Use the same pretreatment method in the subsequent cycle.</th>
</tr>
</thead>
</table>
| Moderate symptoms: any symptoms (mild) not listed above or below (severe), such as: the whole body itching, redness, skin rashes, breathing | Stop infusion.  
Antihistamines and corticosteroids (i.v.)  
Complete the infusion when the symptoms recovers  
Use antihistamines and corticosteroids (i.v.) in the subsequent cycle before the treatment. |
difficulties, low blood pressure when the systolic blood pressure > 80 MMHG

<table>
<thead>
<tr>
<th>Severe symptoms, such as bronchospasm, general urticaria, low blood pressure, systolic blood pressure, &lt;80 MMHG or angioedema</th>
<th>Stop infusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Antihistamines and corticosteroids</strong> (i.v.)</td>
</tr>
<tr>
<td></td>
<td>Add adrenaline, bronchodilator and/or macromolecular liquid i.v. drip when it is necessary</td>
</tr>
<tr>
<td></td>
<td><strong>Termination of the treatment.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NCI-CTCAE V3.0 Grade 4</th>
<th><strong>Termination of the treatment</strong></th>
</tr>
</thead>
</table>

**Antihistamines:**

- **Dexchlorpheniramine** (* i.v. 5-10 mg
- **Diphenhydramine** (* i.v. 25-50mg
- **Promethazine** (* i.m. 50-100 mg

**Corticosteroids:**

- **DEX** (* i.v. 5-10 mg

**Adrenaline:** 1:1000 diluted (0.01 mg/kg, Max 0.5 mg, H, Repeat every 20 min if necessary)

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7. **STUDY PROCEDURES**

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CONFIDENTIAL
7.1. Screening

See Table 3 for schedule of activities.

7.2. Study Period

See Table 3 for schedule of activities.

7.3. Follow-up Visit

See Table 3 for schedule of activities.

Table 3. Schedules of Study

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Screen/base-line(a)</th>
<th>First-line treatment (Cycle)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>1 2 3 4 5 6 7</td>
<td>-</td>
</tr>
<tr>
<td>Day</td>
<td>-D21 -D14 -D7</td>
<td>D1 D22 D43 D64 D85 D106</td>
<td>Every 2 months</td>
</tr>
<tr>
<td>Visit</td>
<td>Visit 1 Visit 2 Visit 3 Visit 4 Visit 5 Visit 6 Visit 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Informed consent
- Random
- Demographic data
- Medical history
- ECG
- Chest X-ray
- Ultrasound
- Routine urine test
- Beta-HCG

Optional (with clinical indications)
### 7.4. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral or administrative reasons. Reasons for trial treatment discontinuation include (further collection data can still go on):

- Disease progression by RECIST as determined by independent radiology review.
- Unacceptable toxicities.
- More than two dose modifications are required.
- Treatment delay for more than 14 days.

<table>
<thead>
<tr>
<th>Neurological examination</th>
<th>Optional (with clinical indications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs</td>
<td>√ √ √ √ √ √ √</td>
</tr>
<tr>
<td>Height and weight</td>
<td>√ √ √ √ √ √ √</td>
</tr>
<tr>
<td>Hematology (d)</td>
<td>√ √ √ √ √ √ √</td>
</tr>
<tr>
<td>Biochemistry(f)</td>
<td>√ √ √ √ √ √ √</td>
</tr>
<tr>
<td>AE and treatment</td>
<td>The whole periods</td>
</tr>
<tr>
<td>Tumor evaluation</td>
<td>√ √ √ √ √ √ √</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>√ √ √ √ √ √ √</td>
</tr>
<tr>
<td>Drug</td>
<td>√ √ √ √ √ √ √</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
</tr>
</tbody>
</table>
- Deterioration of performance status.
- Protocol non-compliance.
- Pregnancy.

Reasons for trial discontinuation include (no further data collection):
- Withdraw of consent
- Patient loss to follow-up.
- Death.
- Study termination.

8. ASSESSMENTS

8.1. Efficacy Assessment

Disease assessments are to be performed as every two cycles of treatment from the date of randomization until radiologic PD has been documented by independent radiology review. Patients who completed 6 cycles and/or discontinued prior to RECIST-defined PD will continue with tumor assessments per protocol until PD has been documented by independent radiology review or patients initiate other anti-cancer treatment. CT or MRI scans should be performed whenever disease progression is suspected. The determination of anti-tumor treatment should be based on RECIST 1.1. The CT or MRI scans should be performed with contrast agents unless contraindicated. All scans will be reviewed by a blinded radiology committee. Tumors assessments must
continue until disease progression has been determined by independent radiologists. Measurable disease lesions located at a previously irradiated area may not considered target lesions.

8.2. Safety Assessments

8.2.1. Adverse Events

Adverse events will be classified by type, incidence, and severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 3.0).

8.2.2. Laboratory Safety Assessment and physical examinations

History and physical examination including: height and weight, Performance status, vital signs (pulse rate, blood pressure, and temperature), neurological examination. Head and neck examination with precise description of lymph node involvement and nasopharyngeal examination.

Hematology: CBC with WBC, differential and platelet count, hemoglobin.

Biochemistry: Alkaline phosphatase, LDH, AST (SGOT), ALT (SGPT), bilirubin, serum creatinine, and calculated clearance, blood electrolytogram.

9. DATA COLLECTION

The data of individual subject is recorded on Electronic Case Report
Form engineered by H&J CRO International, Inc. The content of each CRF is designed to capture the essential information for documentation of the patient demographics, disease status before, during and after treatment, toxicities, disease related symptoms, treatment response, dose adjustment.

10. DATA ANALYSIS/STATISTICS CONSIDERRATION

10.1. Sample Size Determination

The primary end point of this study is progress free survival (PFS). The study aims to prove the superiority of GP over FP in prolonging PFS. As reported previously, the PFS of recurrent or metastatic NPC patients is about 4 months managed with PF regimen [22-26] and about 6 months with GP regimen. Under 80% power and a two-sided 5% significance level, hazard ratio (HR) of 0.67, an enrolment period of 2 years and a follow-up period of 1 year, and taking into account of 5% drop-out rate, and at least 198 PFS events, a total of 362 patients would be required for the study.

10.2. Definitions of Efficacy Assessments

10.2.1. Time to Event Endpoints

Progression free Survival (PFS) is defined as time from randomisation to the date of disease progression as determined by independent radiology review, death from any causes, whichever came
first. PFS will censored on the date of the last evaluable tumor assessments documenting absence of progressive disease for patients who are alive, on study and progression-free at the time of analysis. PFS probability at 6-month, 12-month, and 18-month will be determined. Overall Survival (OS) is defined as the time from randomisation to the time of death from any causes. For patients still alive at the time of analysis, the OS time will be censored on the last day of the patients known to be alive. OS probability at 6-month, 12-month, and 18-month will be determined.

10.2.2. Response Rate Endpoints

ORR is defined as the proportion of patients with complete response (CR) or partial response (PR) according to RECIST 1.1 as determined by independent radiologists, relative to the total population of randomized patients. DCR is defined as the proportion of patients with complete response (CR) or partial response (PR) or stable disease (SD) according to RECIST 1.1 as determined by independent radiologists, relative to the total population of randomized patients. The response assessment will be performed every 2 cycles and should be confirmed 4 weeks later if the patients get CR or PR. Patients who do not have an on-study assessment will be included as not-evaluable.

10.3. Analysis Population

10.3.1. Intention-to-treat Population (ITT)
The ITT population include all patients who are randomized with study drug assignment designated according to initial randomization. The ITT analysis will be the primary population for the evaluation of time-to-event efficacy endpoints (PFS, OS), ORR, and patients’ characteristics.

10.3.2. Safety Analyses Population

The Safety analyses population will include those who receive at least one dose of study medication, with treatment assignments designated according to actual study treatment received. The safety analyses population will be the primary population for evaluating treatment safety.

10.3. Efficacy Analyses

The primary analyses of efficacy endpoints dependent on disease assessments (PFS, ORR, and DCR) will be performed for all randomized patients based on independent radiology review.

10.3.1. Analysis of Primary Endpoints

PFS will be summarized in the ITT population using Kaplan-Meier method by treatment arms. PFS curves will be display graphically. Differences in median PFS between treatment arms will be analyzed by the log rank test. The median event time and corresponding two-sided 95% CI will be provided for each treatment arm. The Cox regression model will be used to estimate the hazard ratio (GP/FP) and 2-sided 95% CI will be provided. Prespecified subgroups included cancer stage
(recurrent or primary metastasis), gender, age ($\leq 50$ vs. $>50$ years), histology, smoking history, prior usage of 5-FU (no vs. yes), and completion of drug cycles ($\leq 4$ vs. $5$ vs. $6$).

### 10.3.2 Analyses of SecondaryEndpoints

OS will be summarized in the ITT population using Kaplan-Meier method by treatment arms. OS curves will be displayed graphically. Differences in median PFS between treatment arms will be analyzed by the log rank test. The median event time and corresponding two-sided 95% CI will be provided for each treatment arm. The Cox regression model will be used to estimate the hazard ratio (GP/FP) and 2-sided 95% CI will be provided. The best response (CR, PR, SD or PD) per RECIST 1.1 will be summarized by treatment arms. ORR and DCR will be compared using a logistic regression model, with the corresponding odds ratio (GP/FP) and 2-sided 95% CI. The 6-month, 12-month, 18-month survival probabilities will be determined using the Kaplan-Meier method.

### 10.3.3 Analyses of Other Endpoints

Descriptive statistics will be used to summarize all patients’ characteristics, treatment administration, efficacy endpoints, and safety parameters.

### 10.4 Independent Radiology Review

The radiographic images will be evaluated by an independent radiology committee to assess tumor status and to determine response and
11. ETHICAL AND ADMINISTRATIVE CONSIDERATION

11.1. Ethical aspects

The study will conform to the articles of the Helsinki declaration as formulated by the 18th World Medical assembly in 1964 and revised by the 29th World Assembly held in Tokyo in 1975 and 41st World Medical Assembly held in Hong Kong in 1989. The investigator must obtain approval from an independent Ethics Committee. The investigator is responsible to explain to the patients participating in the trial about the protocol of the study, and alternative standard treatment available. Patients have rights to refuse participating in the study and investigator must ensure that the patient continue to receive conventional standard treatment appropriate for the clinical condition. All enrolled patients have the rights to withdraw their consent to the study.

11.2. Informed consent

Only after the investigator has explained detail about the clinical study, the patient may sign the informed consent form. The informed consent form must be approved by the Ethics Committee. The informed
consent form is available in Chinese.

11.3. Protocol modifications

The protocol, once signed, cannot be modified in any way without previous agreement between the investigator and the sponsor. Any changes effectuated in the protocol must be reported in writing, dated, signed by both parties, and attached to the original protocol. Such amendments will be submitted for approval to the Ethics committee of Cancer Center of Sun Yat-sen University.
Reference


[21]


[23]. 袁贤彬与冯国生, GP 和 FP 治疗转移性鼻咽癌的疗效观察. 现


[26]. 招丽蓉, et al., 4 种化疗方案治疗晚期鼻咽癌的临床观察. 中国癌症防治杂志, 2010. 02(2).
12. ATTACHMENTS

12.1 ECOG Performance Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic (Fully active, able to carry on all predisease activities without restriction)</td>
</tr>
<tr>
<td>1</td>
<td>Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, &lt;50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, &gt;50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)</td>
</tr>
<tr>
<td>4</td>
<td>Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

12.2 NCI Common Toxicity Criteria for Adverse Events, version 3.0

(NCICTCAE, version 3.0)

12.3. Detailed Methods of cisplatin Hydration, anti-emesis and Chemotherapy.

CISPLATIN HYDRATION

<table>
<thead>
<tr>
<th>1. HYDRATION</th>
<th>Drug</th>
<th>Dose</th>
<th>Methods</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5% GS</td>
<td>1500ml</td>
<td>i.v.drip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9% NS</td>
<td>1000ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium sulfate</td>
<td>2.5 g</td>
<td></td>
<td>day 0 - day 2</td>
</tr>
<tr>
<td></td>
<td>Potassium chloride</td>
<td>2g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamin C</td>
<td>2000mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Diuresis

|              | 20%Mannitol | 150ml  | bid | i.v.drip, BID | day1 |
|              | Furosemide  | 20mg   |     | i.v., QD     | day1 |

3. Cisplatin in chemotherapy

|              | Cisplatin  | 80mg/m²| i.v.drip 3h | Day1 |
|              | 0.9% NS    | 500ml  |            |      |
|              | 0.9% NS    | 100ml  | i.v.drip, washpipe | Day1 |

ANTI-EMESIS

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Drug</th>
<th>Dose</th>
<th>Methods</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>Drug</td>
<td>Dose</td>
<td>Methods</td>
<td>Time</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------</td>
<td>------------</td>
<td>-----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>GP</td>
<td>GEM</td>
<td>1000mg/m2</td>
<td>i.v.drip, within</td>
<td>Day1, Day8</td>
</tr>
<tr>
<td></td>
<td>0.9% NS</td>
<td>100ml</td>
<td>30 min</td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>5-FU</td>
<td>1000mg/m2*4</td>
<td>CIV, continue</td>
<td>Day1-Day5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>days</td>
<td>96h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9% NS</td>
<td>Defined amount</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>