Maintenance Capecitabine Plus Best Supportive Care Versus Best Supportive Care for Metastatic Nasopharyngeal Carcinoma: A Randomised, Phase 3 clinical trial

FINAL PROTOCOL

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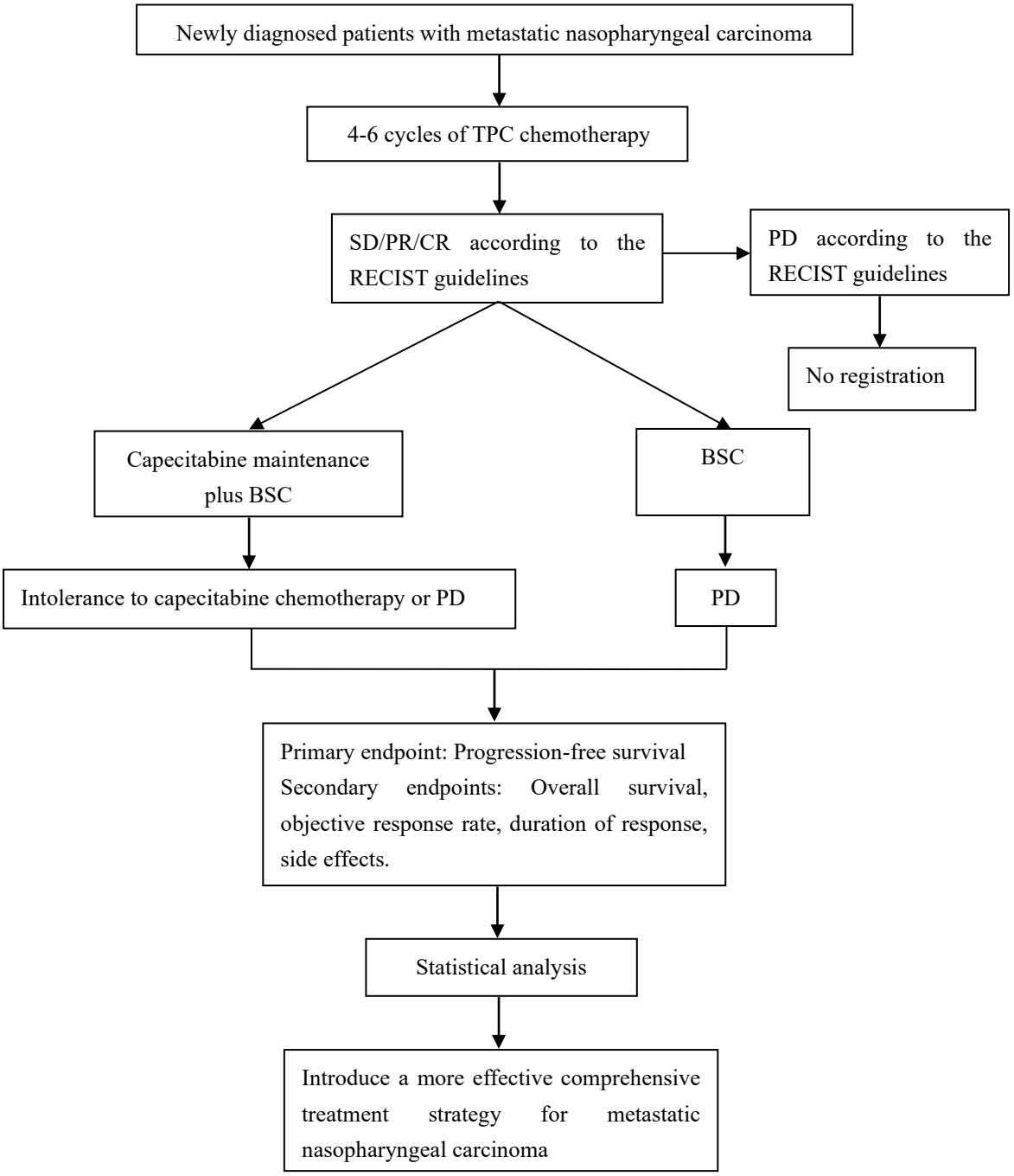
SCHEMA


Newly diagnosed patients with metastatic nasopharyngeal carcinoma
4-6 cycles of TPC chemotherapy
SD/PR/CR according to the RECIST guidelines
PD according to the RECIST guidelines
No registration
Capecitabine maintenance plus BSC
BSC
Intolerance to capecitabine chemotherapy or PD
PD
Primary endpoint: Progression-free survival
Secondary endpoints: Overall survival, objective response rate, duration of response, side effects.
Statistical analysis
Introduce a more effective comprehensive treatment strategy for metastatic nasopharyngeal carcinoma

1·0 Background

Nasopharyngeal carcinoma is one of the most common head and neck cancers and prevalent in southeast Asia and north Africa. Nasopharyngeal carcinoma remains an important cause of cancer-related death worldwide with an incidence of approximately 50,000 deaths annually.[1] For patients with metastatic disease, platinum-based combination chemotherapy results in a response rate of 50% to 70% and a median survival time of approximately 20 months.[2] Chemotherapy is typically administered for approximately 6 cycles and then discontinued, given concerns for cumulative toxicities in the setting of diminishing benefit.[3] However, the vast majority of patients experience disease progression soon after completing first-line chemotherapy, with a median progression-free survival of approximately 3 months.[4]

Maintenance treatment with low-dose chemotherapeutic agents aims to extend clinically meaningful survival by delaying disease progression and to prolong the period between chemotherapy treatments, thereby allowing patients to avoid the associated toxicities that can affect quality of life.[5] Recently, an extensive body of research has emerged concerning maintenance therapy in malignant tumours, and maintenance therapy after chemotherapy may be an attractive strategy for both scientific and pragmatic reasons.[6,7] The role of maintenance cytotoxic therapy in metastatic nasopharyngeal carcinoma remained unclear. Capecitabine is an oral fluoropyrimidine agent that can mimic the pharmacokinetics of infusion 5-fluorouracil directed against tumours, and is associated with lower incidence of complications, such as diarrhea, stomatitis, nausea, and neutropenia, than infusion 5-fluorouracil.[8] Capecitabine has been proved as an effective maintenance drug, either alone or in combination, in colorectal and breast malignancies, with additional benefits of improved tolerance and convenience.[8-10] Fluoropyrimidines have evidence of activity in nasopharyngeal carcinoma.[11] Capecitabine is a potentially suitable agent for maintenance therapy because its toxicity profile is favorable and without cumulative effects.[12]

Therefore, a randomised, phase 3 trial was designed to investigate whether maintenance therapy with capecitabine plus best supportive care (BSC) therapy would improve progression-free survival for patients with metastatic nasopharyngeal carcinoma who achieved disease control after 4–6 cycles of TPC (taxol, cisplatin and capecitabine) palliative chemotherapy compared with BSC alone.

2·0 Objectives

2·1 Primary objective

This study is designed to evaluate and compare the progression-free survival between the

capecitabine maintenance therapy plus BSC and BSC alone in newly diagnosed metastatic nasopharyngeal carcinoma patients after 4–6 cycles of TPC palliative chemotherapy.

2·2 Secondary objectives

To evaluate and compare overall survival, duration of response, objective response rate, adverse effects, and quality of life between the capecitabine maintenance therapy plus BSC and BSC alone in newly diagnosed metastatic nasopharyngeal carcinoma patients after 4–6 cycles of TPC palliative chemotherapy.

3·0 Subject Enrollment

3·1 Eligibility criteria

3·1·1 Firstly diagnosed metastatic nasopharyngeal carcinoma patients

3·1·2 Disease controlled after 4–6 cycles of palliative chemotherapy with taxol, cisplatin and capecitabine.

3.1.3 Age 18–65 years.

3·1·4 Eastern Cooperative Oncology Group performance status of 0 or 1.

3·1·5 Life expectation at least 12 weeks.

3·1·6 No systemic chemotherapy within 6 months, except for induction chemotherapy or concurrent chemotherapy.

3·1·7 With at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumours version 1·1 (RECIST 1·1).

3·1·8 Adequate organ function:

-White blood cell count of ≥4·0×10^9/L; absolute neutrophil count of ≥2·0×10^9/L;

-Hemoglobin concentrations of ≥90 g/L; platelet cell count of ≥100×10^9/L;

-Aspartate transaminase (AST) and alanine transaminase (ALT) of <2·5 times the upper limit of the normal;

-Creatinine clearance rate of >60 mL/min.

3·1·9 Signed informed consent.

3·2 Exclusion criteria

3·2·1 Severe heart disease.

3·2·2 HIV infection.

3·2·3 Severe infection.

3·2·4 Brain metastasis, except for patients who received radical therapy 6 months ago and were stable in 4 weeks.

3·2·5 Allogeneic organ transplantation.

3·2·6 Malignancy other than nasopharyngeal carcinoma, except: cervical carcinoma in situ, cured basal cell carcinoma, bladder cancer of Ta, Tis or T1, or any cured cancer for at least 3 years.

3·2·7 Pregnancy or lactation.

3·2·8 Difficulty in swallowing.

3·2·9 Received other test drugs.

3·3 Criteria for withdrawal from protocol treatment

3·3·1 Disease progression.

3·3·2 Unacceptable toxicity. The reason(s) must be recorded.

3·3·3 Intercurrent diseases which may affect assessments of clinical status to a significant degree and require discontinuation of drug, or both.

3·3·4 The patient may withdraw from the study at any time for any reason. The reason should be recorded.

4 Treatment Plan

4·1 Chemotherapy

4·1·1 Cisplatin, taxol plus capecitabine regimen

Cisplatin is intravenously given at dose of 60 mg/m^2 on day 1 and once every 3 weeks for maximum of 6 cycles. Taxol is intravenously given at dose of 150 mg/m^2 on day 1 and once every 3 weeks for maximum of 6 cycles. Capecitabine 1,000 mg/m^2 orally twice daily on days 1–14 and once every 3 weeks for maximum of 6 cycles.

4·1·2 Administration

To prevent the nephrotoxic effects of cisplatin, we apply a 4-day hydration protocol before and during the administration of cisplatin (days 1–3) and used furosemide (day 1) and mannitol (days 1–2). We use antiemetic drugs, such as the 5-HT3-receptor antagonist dexamethasone, to prevent chemotherapy-induced nausea and vomiting.

4·1·3 Capecitabine maintenance therapy and best supportive care

Capecitabine maintenance therapy is 1,000 mg/m^2 orally twice daily on days 1–14 and once every 3 weeks for maximum of 2 years.

BSC is defined as those measures designed to provide palliation of symptoms and improve quality of life as much as possible.

*If severe tumor compression and destruction symptoms occur during follow-up, including severe pain, pathological fracture, etc., then according to the clinical needs to control local symptoms and improve quality of life, the appropriate treatment will be provided, including surgery, RT and local chemotherapy (e.g., TACE for the treatment of liver metastases)

4·1·4 Dosage adjustments

4·1·4·1 Dose adjustment for hematologic adverse events

Dose adjustment for hematologic toxicity				
Absolute neutrophil count		Platelet count	Cisplatin dose adjustment	Taxol dose adjustment
>1·50×10^9/L	And	>75·00×10^9/L	Full dose	Full dose
1·00-1·49×10^9/L	And/or	50·00-74·99×10^9/L	Full dose	Full dose
<1·00×10^9/L	And/or	<50·00×10^9/L	80%	90%

4·1·4·2 Dose adjustment for non-hematologic adverse events

Dose adjustment for renal toxicity				
Absolute creatinine		Creatinine clearance rate	Cisplatin dose adjustment	Taxol dose adjustment
≤ 1·5×upper normal value	And	≥50 mL/min	Full dose	Full dose
>1·5×upper normal value	And/or	40-50 mL/min	80%	Full dose
>1·5×upper normal value	And/or	<40 mL/min	Withhold drug	Withhold drug

Hepatic toxicity	Dose adjustment
AST/ALT >2·5 – ≤5×ULN and/or alkaline phosphatase (ALP) >2·5 – ≤ 5×ULN	Decrease 1 level

and/or bilirubin > 1 – ≤2×ULN	
AST/ALT >5×ULN and/or ALP >5×ULN and/or bilirubin >2×ULN	Stop chemotherapy

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Gastrointestinal toxicity		Dose adjustment
Grade 3	First episode	Full dose
	Second episode	Decrease 1 level
Grade 4	Stop chemotherapy	

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Peripheral neuritis		limb joint muscle pain	Taxol dose adjustment
level 2	Or	level 2	80%
level 3	Or	level 3	Withhold drug
level 4	Or	level 4	Withhold drug

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177 **4·1·4·3** Local label should be used for capecitabine dose modifications for the management of
178 adverse reactions

Toxicity*	During a course of therapy	Dose adjustment for next treatment (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently.	-
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	75%
2nd appearance		50%
3rd appearance		-

Grade 4		
1st appearance	Discontinue permanently	50%, if the physician deems it to be in the patient's best interest to continue
*Common Terminology Criteria for Adverse Events v4.0 or toxicity management per local label was used, except for the hand-foot syndrome		

4·2 Salvage therapy

The choice of suitable for local treatment is made by investigators' discretion, providing a deemed clinical benefit. Local treatment for metastatic lesions, including definitive radiotherapy, surgical resection, ablation, or other treatments are used for some patients to control local symptoms and eliminate metastases in the bone, liver, lungs, or other organs. Second- or third-line chemotherapy will be provided for patients with disease progression.

5·0 Observation and Assessment

During the initial screening period, eligible metastatic nasopharyngeal carcinoma patients are treated with TPC regimen. Every 2 cycles of chemotherapy, an efficacy evaluation will be performed. The patients who are evaluated to achieve disease control after 4–6 cycles of chemotherapy will be officially registered.

5·1 Before treatment

All patients are under standardized management for nasopharyngeal carcinoma, and they need to perform a series of examinations as well as provide relevant information to confirm pathologic diagnosis and clinical stage before admitted into trial:

5·1·1 Medical history review

5·1·2 Personal data collection

5·1·3 Review of present medications and treatment

5·1·4 Body examinations, include height, weight and vital signs

5·1·5 Physical examination of head and neck region, include nasopharynx and cervical lymph nodes

5·1·6 Physical examination of the nervous system

5·1·7 Nasal endoscopy and lesion biopsy

5·1·8 Biopsy or needle aspiration of distant metastases

5·1·9 Blood routine.

5·1·10 Epstein-Barr virus (EBV) serologic tests (EBV antibodies, EBV DNA was optional, depending on the laboratory availability of the participating centres).

5·1·11 Urine routine.

5·1·12 Imaging, including enhanced magnetic resonance imaging (MRI) or enhanced computed tomography (CT) of the head and neck (CT is indicated only in patients with contraindication to MRI)

5·1·13 Chest film or CT

5·1·14 Emission computed tomography bone scan

5·1·15 Abdominal ultrasonography or CT

5·1·16 Positron emission tomography (PET)/CT is optional and is performed at the discretion of the attending physician

5·1·17 Signed informed consent

5·2 Screening confirmation period

5·2·1 PET-CT, MRI and/or CT of the primary tumour and distant metastases, which is performed after treatment, and complete response, partial response, stable disease, or progressive disease is evaluated according to RECIST 1·1.

5·2·2 Physical examinations of the head and neck region, including the nasopharyngeal and cervical lymph nodes

5·3 During treatment

The following aspects need to be assessed from the start to the end of treatment.

5·3·1 MRI and/or CT of the primary tumour and distant metastases, which is performed after treatment, and complete response, partial response, stable disease, or progressive disease is evaluated according to RECIST 1·1.

5·3·2 General conditions

5·3·3 Acute and late toxicities assessment (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4·0), including for hematological toxicity, gastrointestinal reactions, nephrotoxicity, mucositis, neurotoxicity, etc.

5·3·4 Laboratory tests: blood routine and blood biochemistry are required within 1 week prior to each cycle of chemotherapy and once per week during treatment.

6 Follow-Up and Recording of Events

After completing treatment, the patients are followed up every 2 to 3 months until death to evaluate the patients' recent and long-term efficacy and safety profiles. Follow-up method: Record of the patient's examination data, a doctor's letter with signature to document the visit, or a doctor's follow-up records collected by telephone Follow-up content: Routine examination of the nasopharyngeal lesions and lymph nodes, and B-mode ultrasound, chest X-ray, and CT or MR examinations of the distant metastases every 3 months. PET/CT or bone scintigraphy are performed when clinically indicated. The treatment responses are also evaluated according to the RECIST criteria.

All patients will be followed-up until death and cause of death recorded. Deaths due to unknown cause are counted as death due to nasopharyngeal carcinoma if disease is still present at last assessment.

7 Safety Measures and Quality Control

7·1 Provide a systemic learning program for every member in the research group Assigned one doctor in each centre to lead tumour staging, which must be in accordance with the 7th edition of American Joint Committee on Cancer guidelines and to ensure that every patient enrolled is eligible. Patients are assigned to their groups based on random numbers.

7·2 Make a monitoring plan of adverse effects and emergency plan.

7·3 Research plan is made by all participating centres and approved by Ethics Committee.

7·4 Develop all kinds of standard operation procedures related to this study.

7·5 Establish standardized evaluation system to unify diagnostic criteria, curative effect judging criteria, etc.

7·6 Establish professional statistical plan.

7·7 Research staffs are trained before the study.

7·8 Ensure that every participating centre conducts the study at the same pace.

7·9 Arrange quality controller, make quality control plan and check regularly.

7·10 Set up coordination committee, curative effect judging group and follow-up team.

8·0 Statistical Analysis

8·1 Endpoint definitions

8·1·1 Primary endpoint

The progression-free survival is defined as the time from randomised assignment to disease progression, or death from any cause, whichever occurs first.

8·1·2 Secondary endpoints

8·1·2·1 Overall survival

The overall survival is defined as the time from randomised assignment to the date of death from any cause.

8·1·2·2 Duration of response

The duration of response is defined as the time from the first cycle of palliative chemotherapy to the progression of disease, or death from any cause, whichever occurs first.

8·1·2·3 Objective response rate

Treatment response is assessed by imaging by independent image committee every two cycles until disease progression. Tumour response is classified according to the RECIST criteria, version 1.1. Complete response is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have been reduced in the short axis to <10 mm. Partial response is defined as an at least 30% decrease in the sum of diameters of the target lesions, with the baseline diameter sum serving as the reference. Progressive disease is defined as an at least 20% increase in the sum of diameters of the target lesions, with the smallest sum during study serving as the reference (including the baseline sum). In addition to a relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Stable disease is defined as both insufficient size reduction to qualify as partial response and an insufficient increase to be considered progressive disease, with the smallest diameter sum during the study serving as the reference.

8·1·2·4 Adverse events

Adverse events refer to any adverse medical events that occur on the patient. They do not necessarily have a causal relationship with treatment. Investigators should keep a detailed record of any adverse events that occur in the patients. The record of adverse events shall include a description of the adverse events, the time of occurrence, severity, duration, measures taken, and the final outcomes. Investigators should assess the possible association between the adverse events and the tested drugs

according to the five-level classification of "positive relevance, possible irrelevance, positive irrelevance, and inability to determine." Acute toxicities are assessed according to NCI-CTCAE v4·0. Acute toxicities include hematological toxicity, mucositis, allergic reactions and other adverse events and serious adverse events.

8·1·2·5 Quality of life

EORTC QLQ-C30 and QLQ-H&N35 (v1·0) are used to assess life quality of patients, and the change of their life quality is recorded and evaluated weekly (Week 1-6) from before the beginning of treatment to end, 3 months, 6 months, and 1 year after chemotherapy.

8·2 Sample size estimation

The trial used a two-sided 5% type I error and had 80% power to detect an improvement in progression-free survival from 6 months in the BSC group to 11 months in the maintenance group, which corresponded to a hazard ratio of 0·55 in median progression-free survival.[2,13] In view of these assumptions, the design was powered for 98 patients to be randomly assigned in 48·0 months with an additional 12·0 months of follow-up. After considering a 5% dropout rate, we estimated that a total of 104 patients (52 patients in each group) were required.

8·3 Stratification/Randomisation scheme

8·3·1 Stratification

Patients are stratified according to treatment centres.

8·3·2 Randomisation

Eligible patients are randomised using a 1:1 allocation of patients to either capecitabine maintenance therapy plus BSC (maintenance group) or BSC alone (BSC group). The randomised block design is conducted by SYSUCC and block size will be chosen by the statistician (Prof. Qing Liu) so that each block contains the patients in equal proportion. This procedure helps to ensure both randomness and investigator blinding (the block sizes are known only to the statistician), as recommended by Friedman et al (Friedman J, Furberg, C, DeMets D. Fundamentals of clinical trials. New York: Springer-Verlag; 1998). Randomisation will be generated by the statistician in opaque, sealed envelopes, labeled by stratum, which will only be unsealed after patient registration. Patients will be identified by a unique subject number that will remain constant for the duration of the study.

8·4 Data management

All information about the enrolled patients after registration will be sent to Sun Yat-Sen University

Cancer Centre for management. To monitor the study and make decisions with respect to possible early closure and publication, we will appoint an independent Data Monitoring Committee.

The independent Data Monitoring Committee will meet at least once per year (or will have discussions via electronic means) to ensure no excessive toxicity and to monitor the quality of the data and the results. Until it is decided to release the results, only the independent Data Monitoring Committee will be allowed access to the data.

8·5 Case report form

The case report form is designed before the study. The case report form is required to record detailed medical history, treatment and follow-up information, and it should be easy to fill in as well as save in database.

8.6 Analytical approach

The results of this study are analyzed by the intention-to-treat approach, and all eligible patients are analyzed according to the randomisation scheme. The Kaplan–Meier estimator is used to estimate the survival function from lifetime data, and log-rank test to compare the difference of survivals between two groups. Response rates and the incidence of toxicities are compared by the chi-square test. Quality of life was analyzed using a mixed effect model. Multiple prognostic factors are analyzed by Cox regression. The statistical test for progression-free survival was one sided, the left statistical tests were two-sided, and a p value of less than 0·05 was considered statistically significant.

9·0 Ethical Considerations

9·1 This study must be approved by an appropriate institutional ethic committee.

9·2 An informed consent must be obtained from individual patients. Copy of the Consent Form, contact number of investigator and ethics committee will be available to patient on request.

9·3 All serious and unexpected adverse events or death related to the drugs or radiotherapy must be reported to the study coordinator immediately. Serious adverse events to be reported include all deaths during or within 30 days of protocol treatment regardless of cause, grade 5 toxicity, life-threatening grade 4 toxicity, and/or unexpected toxicity. The Study Coordinator of respective centre should complete form and fax this within 24 hours to the Principal Investigator (Dr. Yan-Qun Xiang, Tel: 020-87343379, Fax: 020- 87343392), the centre of clinical trials, the institutional ethic committee and Sun Yat-Sen University Cancer Centre. Together with the Principal Investigator,

appropriate and prompt action will be taken if warranted. Reactions and deaths beyond 30 days from protocol treatment that are judged definitely unrelated to treatment should not be reported.

10 References

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394 metastatic nasopharyngeal carcinoma: a phase II study. *Br J Cancer.* 1999;80(12):1962-
395 1967.

Summary of changes in protocol:

Page	item	Before amendment	After amendment	reason	version
P6-7	Treatment Plan	Capecitabine maintenance therapy is 1,250 mg/m^2 orally twice daily on days 1–14 and once every 3 weeks for maximum of 2 years.	Capecitabine maintenance therapy is 1,000 mg/m^2 orally twice daily on days 1–14 and once every 3 weeks for maximum of 2 years.	Taking into account the patient's completion and tolerance of capecitabine.	Ver.2.0 approved date: May 28, 2016
P13	Sample size estimation	142 subjects will be randomized in a 1:1 fashion (71 in each arm)	104 subjects will be randomized in a 1:1 fashion (52 in each arm)	Considering the influence of duration of enrollment and follow-up on sample size, also too high drop-out rate	Ver.3.0 approved date: May 30, 2018

406 **Appendix I**

407 **ECOG PERFORMANCE STATUS**

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Appendix II

The CTCAE v4.0 manual can be found at the following URL:

http://ctep.cancer.gov/forms/CTCAEv4.pdf.