Nab-paclitaxel, cisplatin, and capecitabine versus cisplatin and gemcitabine as first line chemotherapy in patients with recurrent or metastatic nasopharyngeal carcinoma: randomised phase 3 clinical trial

Guo-Ying Liu,[1,2] Yan-Fang Ye,[3] Yao-Fei Jiang,[1] Gina Jinna Chen,[4] Wei-Xiong Xia,[1] Yi-Sheng Huang,[5] Tian-Sheng Gao,[6] Yi-Min Liu,[2] Ya-Ting Hou,[5] Jian-Fei Li,[5] Jia-Hao Liu,[6] Nian Lu,[7] Chang-Long Chen,[2] Liang-Ru Ke,[7] Hu Liang,[1] Wei-Xin Bei,[1] Wang-Zhong Li,[1] Shu-Hui Dong,[1] Qin Liu,[1] Changqing Xie,[8] He-Rui Yao,[2,9] Yan-Qun Xiang[1]

For numbered affiliations see end of the article

Correspondence to: YQ Xiang xiangyq@sysucc.org.cn (ORCID 0000-0003-4334-3794)

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ABSTRACT

OBJECTIVE

To compare the effectiveness and safety of nab-paclitaxel, cisplatin, and capecitabine (nab-TPC) with gemcitabine and cisplatin as an alternative first line treatment option for recurrent or metastatic nasopharyngeal carcinoma.

DESIGN

Phase 3, open label, multicentre, randomised trial.

SETTING

Four hospitals located in China between September 2019 and August 2022.

PARTICIPANTS

Adults (≥18 years) with recurrent or metastatic nasopharyngeal carcinoma.

INTERVENTIONS

Patients were randomised in a 1:1 ratio to treatment with either nab-paclitaxel (200 g/m^2 on day 1), cisplatin (60 mg/m^2 on day 1), and capecitabine (1000 mg/m^2 twice on days 1-14) or gemcitabine (1 g/m^2 on days 1 and 8) and cisplatin (80 mg/m^2 on day 1).

MAIN OUTCOME MEASURES

Progression-free survival was evaluated by the independent review committee as the primary endpoint in the intention-to-treat population.

RESULTS

The median follow-up was 15.8 months in the prespecified interim analysis (31 October 2022). As assessed by the independent review committee, the median progression-free survival was 11.3 (95% confidence interval 9.7 to 12.9) months in the nab-TPC cohort compared with 7.7 (6.5 to 9.0) months in the gemcitabine and cisplatin cohort. The hazard ratio was 0.43 (95% confidence interval 0.25 to 0.73; P=0.002). The objective response rate in the nab-TPC cohort was 83% (34/41) versus 63% (25/40) in the gemcitabine and cisplatin cohort (P=0.05), and the duration of response was 10.8 months in the nab-TPC cohort compared with 6.9 months in the gemcitabine and cisplatin cohort (P=0.009). Treatment related grade 3 or 4 adverse events, including leukopenia (4/41 (10%) *v* 13/40 (33%); P=0.02), neutropenia (6/41 (15%) *v* 16/40 (40%); P=0.01), and anaemia (1/41 (2%) *v* 8/40 (20%); P=0.01), were higher in the gemcitabine and cisplatin cohort than in the nab-TPC cohort. No deaths related to treatment occurred in either treatment group. Survival and long term toxicity are still being evaluated with longer follow-up.

CONCLUSION

The nab-TPC regimen showed a superior antitumoural efficacy and favourable safety profile compared with gemcitabine and cisplatin for recurrent or metastatic nasopharyngeal carcinoma. Nab-TPC should be considered the standard first line treatment for recurrent or metastatic nasopharyngeal carcinoma. Longer follow-up is needed to confirm the benefits for overall survival.

TRIAL REGISTRATION

Chinese Clinical Trial Registry ChiCTR1900027112

WHAT IS ALREADY KNOWN ON THIS TOPIC

Gemcitabine plus cisplatin prolongs progression-free survival and overall survival compared with 5-fluorouracil plus cisplatin in patients with recurrent or metastatic nasopharyngeal carcinoma

However, median progression-free survival derived from the gemcitabine plus cisplatin regimen remains suboptimal

WHAT THIS STUDY ADDS

This study compared nab-paclitaxel, cisplatin, and capecitabine (nab-TPC) with gemcitabine plus cisplatin as first line treatment in recurrent or metastatic nasopharyngeal carcinoma

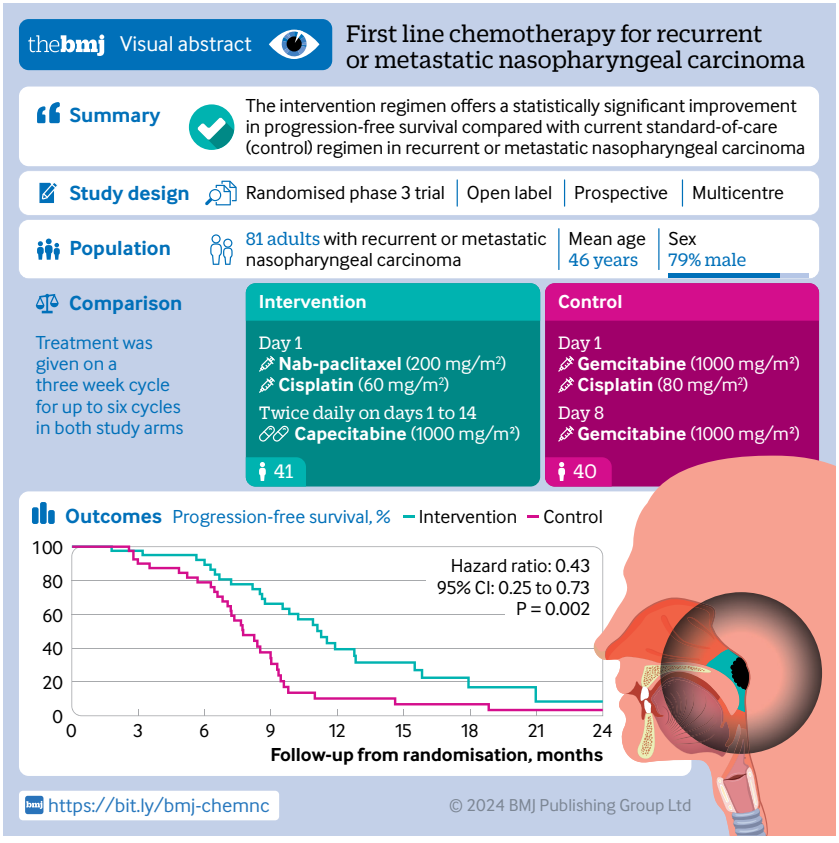
Nab-TPC showed a statistically significant improvement in progression-free survival compared with the current standard-of-care gemcitabine plus cisplatin regimen

The nab-TPC regimen has a manageable safety profile and could become the standard treatment option for patients with recurrent or metastatic nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma is a common malignant tumour in the head and neck cancer spectrum and is particularly prevalent in regions such as southern China, southeast Asia, and north Africa.[1 2] Despite the improved overall survival rate of patients with localised nasopharyngeal carcinoma recently, clinical outcome is still not satisfactory in patients with recurrent or metastatic nasopharyngeal carcinoma.[3-5]

A platinum based chemotherapy regimen is generally recommended as the first line standard of care option for patients with recurrent or metastatic nasopharyngeal carcinoma. A phase 3 study has shown that gemcitabine plus cisplatin prolongs progression-free survival and overall survival in comparison with 5-fluorouracil plus cisplatin, which



led to the establishment of gemcitabine plus cisplatin as the front line regimen for recurrent or metastatic nasopharyngeal carcinoma.[6-8] However, median progression-free survival derived from the gemcitabine plus cisplatin regimen remains limited, ranging from 7.0 to 7.7 months according to data from several prospective clinical studies.[6 7 9] Hence, innovative strategies are needed to enhance clinical benefits while maintaining an acceptable toxicity profile.

Recently, our phase 3 trial reported that capecitabine maintenance after a triplet regimen with taxanes, cisplatin, and capecitabine has tolerable toxicities in patients with metastatic nasopharyngeal carcinoma, as well as enhanced tumour control and prolonged survival.[10] Compared with traditional solvent based paclitaxel, albumin binding paclitaxel is a water soluble paclitaxel linked to an albumin nanoparticle, which increases the concentration and uptake rate of nab-paclitaxel in tumour cells and reduces cytotoxicity and solvent induced anaphylaxis.[11 12] The combination of nab-paclitaxel and cisplatin has been approved for the treatment of metastatic nasopharyngeal carcinoma on the basis of satisfactory efficacy (median progression-free survival 9 months) and moderate toxicity.[13] We designed this phase 3, open label, randomised trial to evaluate the efficacy and safety of nab-paclitaxel, cisplatin, and capecitabine (nab-TPC) as first line treatment for recurrent or metastatic nasopharyngeal carcinoma compared with a gemcitabine plus cisplatin regimen.

Methods

Study design

This was a multicentre, open label, randomised, controlled, phase 3 study conducted in eligible patients at four hospitals located in China (supplementary table A). Figure 1 shows a flowchart illustrating the study design. All patients signed written informed consent before enrolment.

Participants

Patients were eligible if they had histological or cytological confirmation of nasopharyngeal carcinoma. Other key inclusion criteria included primary metastatic disease or metastatic disease after curative radiotherapy, no previous receipt of systemic therapy for metastatic disease, Eastern Cooperative Oncology Group performance status of 0 or 1, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), adequate organ function, an estimated life expectancy of at least 12 weeks, and age ≥18 years. We excluded patients with a history of other malignancies, central nervous system metastases, severe coexisting illness, or pregnancy. The complete eligibility criteria are given in the trial protocol, available as an online supplement.

Randomisation and masking

A computer generated random number code was provided for randomisation of enrolled patients at the Sun Yat-sen University Cancer Center. Random distribution sequences were generated using a permuted block of flexible size (2, 4, 6, or 8), with no stratification factors. Randomisation details were provided in sequentially numbered, opaque, sealed envelopes prepared by a data management team unaware of the patient assignment process. The therapy assignment was not masked to investigators, patients, and other treating oncologists, but the central evaluation of the imaging data by an independent review committee was done in a masked manner.

Procedures

Before randomisation, patients received a comprehensive screening assessment within four week intervals between enrolment and start of treatment. Eligible patients were randomly assigned (1:1) to the nab-TPC or gemcitabine plus cisplatin cohort. Patients assigned to the nab-TPC cohort received nab-paclitaxel (200 mg/m^2) on day 1, cisplatin (60 mg/m^2) on day 1, and capecitabine (1000 mg/m^2 twice daily) on days 1-14 of each three week cycle for up to six cycles, followed by capecitabine maintenance for a maximum of two years. Patients assigned to the gemcitabine plus cisplatin cohort received gemcitabine (1g/m^2) on days 1 and 8 and cisplatin (80 mg/m^2) on day 1 of every three week cycle for up to six cycles, followed by best supportive care. Trial assigned chemotherapy was continued until progression of disease, intolerable toxicity, investigator's decision, or withdrawal of consent, whichever occurred first. Crossover between the two chemotherapy regimens was permitted at

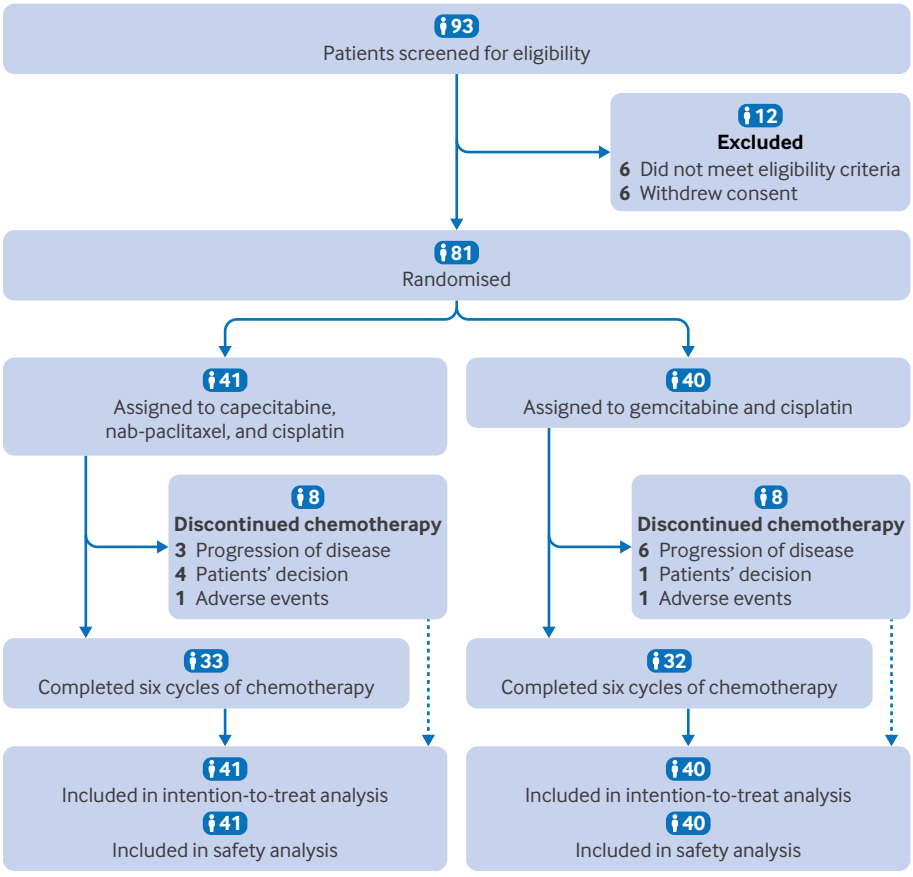


Fig 1 | Consort diagram of study

disease progression. Details of the pretreatment screening evaluations and chemotherapy dose modifications during the trial are available in the trial protocol.

We assessed radiological responses of tumours every six weeks during the course of chemotherapy and every 12 weeks thereafter, according to RECIST v1.1, with 18F-fluorodeoxyglucose positron emission tomography-computed tomography or enhanced magnetic resonance imaging or computed tomography scan. We used the National Cancer Institute Common Terminology Criteria, version 4.0, to evaluated adverse events during treatment and for a period of 90 days after the last dose of study medication.

Endpoints

Progression-free survival served as the primary endpoint, which we assessed as the time from randomisation to disease progression according to RECIST v1.1 evaluated by the independent review committee, or death, whichever occurred first. Secondary endpoints consisted of overall survival, objective response rate, and safety. We defined overall survival as the time from randomisation to death from any cause and the objective response rate as the proportion of patients showing a best overall response, including complete and partial response.

Statistical analysis

We derived the sample size from the previously reported median progression-free survival (7.0 months) in a phase 3 trial in the setting of patients with recurrent or metastatic nasopharyngeal carcinoma treated with a gemcitabine plus cisplatin regimen as the first line option.[7] We calculated that we would need to randomise approximately 134 patients (67 patients per group), providing 80% power to detect the underlying hazard ratio of 0.42 for the primary analysis of progression-free at a two sided α level of 5% with one interim analysis. An interim analysis of progression-free survival, as prespecified, was conducted approximately three years after the first patient was randomised.

We did all analyses within the intention-to-treat population. Safety analyses included all patients who received at least one dose of the study treatment. We presented continuous variables as medians with interquartile ranges and compared them by using the Mann-Whitney test. We assessed categorical variables by using either the χ^2 test or Fisher's exact test for comparison. We estimated survival curves and rates for time-to-event endpoints (overall survival, progression-free survival, and duration of response) by using the Kaplan-Meier method. We used stratified log-rank tests to compare survival between the two treatment cohorts.

We used a Cox proportional hazards model to calculate hazard ratios and their corresponding 95% confidence intervals, with stratification according to the study design. We verified the assumption of proportional hazards by examining the Schoenfeld residuals. In addition, we did post hoc subgroup analyses stratified by various factors, including age (<50 *v* ≥50 years), gender (male *v* female), smoking history (yes *v* no), cancer stage (primary metastases *v* recurrent), number of metastatic organs (1 *v* ≥2), presence of liver metastasis (present *v* absent), presence of lung metastasis (present *v* absent), presence of bone metastasis (present *v* absent), and levels of Epstein-Barr virus DNA (<2000 *v* ≥2000 copies/mL). We tested treatment-by-covariate interaction by using the Cox proportional hazards model as the basis for the interaction study.

The progress of trial was overseen by an independent data monitoring committee, empowered to determine whether early termination of the trial was warranted. To uphold an overall type I error rate of 0.05 throughout the trial, early termination followed the O'Brien-Fleming type boundary (with an α level of 0.005). An interim analysis done on 31 October 2022 led the independent data monitoring committee to terminate the trial on the basis of the findings. This report presented the data of survival and adverse events.

We used R software (version 4.0.5) and SPSS (version 24.0) for statistical analyses. The codes used for analysis are provided as an online supplement. We deemed a significance threshold of 0.05 or lower for two sided P values to indicate statistical significance.

Patient and public involvement

Although not initially involved in designing the trial, all participants were informed of the trial's objectives and contents on recruitment. Patients were not involved in the study's execution or subsequent report preparation. When we began the research, patient and public participation was not a routine practice in our specialty in this region.

Results

Patients

Between October 2019 and August 2022 a total of 81 eligible patients with recurrent or metastatic nasopharyngeal carcinoma across four hospitals were randomly assigned to treatment with either nab-TPC (n=41) or gemcitabine plus cisplatin (n=40) (fig 1). Baseline demographics and disease characteristics were balanced between the treatment groups (table 1). The median age was 48 (interquartile range 36-57) years, and 79% of patients were male. Non-keratinising carcinoma was predominant among the patients (98%). Approximately two thirds of patients had previously undergone induction and concurrent chemoradiotherapy, and all patients had distant metastases. Thirty three (80%) patients in the nab-TPC cohort and 33 (83%) patients in the gemcitabine plus cisplatin cohort received six cycles of chemotherapy. The initial cost for each group is shown in supplementary table B.

After progression was documented, more than half of the patients received second line or third line chemotherapy, with 23 (56%) patients in the nab-TPC cohort and 26 (65%) patients in the gemcitabine plus cisplatin cohort receiving such treatment (supplementary table D). The predominant regimen used was anti-programmed cell death protein-1 inhibitor, administered to 21 (51%) patients in the nab-TPC cohort and 20 (50%) patients in the gemcitabine plus cisplatin cohort. Additionally, a portion of patients in both cohorts received crossover treatment—12 (29%) in the nab-TPC cohort and 12 (30%) in the gemcitabine plus cisplatin cohort.

Efficacy

As of the interim analysis cut-off date (31 October 2022), the median follow-up period was 15.8 (interquartile range 11.6-24.9) months. For the primary endpoint of progression-free survival, as evaluated independently, 27 (66%) of 41 patients in the nab-TPC cohort and 32 (80%) of 40 patients in the gemcitabine plus cisplatin cohort had disease progression or died. The median progression-free survival was 11.3 (95% confidence interval 9.7 to 12.9) months for the nab-TPC cohort and 7.7 (6.5 to 9.0) months for the gemcitabine plus cisplatin cohort. The difference in median progression-free survival between the two cohorts was statistically significant (hazard ratio 0.43, 95% confidence interval 0.25 to 0.73; P=0.002) (fig 2). The proportional hazards assumption for progression-free survival was unmet (supplementary figure A). In multivariate analyses, treatment group was an independent prognostic factor for progression-free survival (supplementary table F). For patients whose pre-treatment Epstein-Barr virus DNA was ≥2000 copies/mL, the nab-TPC regimen significantly improved their progression-free survival (hazard ratio 0.42, 0.21 to 0.84; P=0.01, supplementary figure B). However, this survival benefit was not observed for patients whose pre-treatment Epstein-Barr virus DNA was <2000 copies/mL (hazard ratio 0.45, 0.17 to 1.19; P=0.11). Improvement in progression-free survival was consistent in patients with or without liver metastases (supplementary figure C). Figure 3 shows the outcomes of the primary endpoint, independently assessed progression-free survival, in the primary analyses for post hoc subgroups.

In the updated analysis done on 3 June 2023, we found that 31 (76%) patients in the nab-TPC cohort and 35 (88%) patients in the gemcitabine plus cisplatin cohort had experienced disease progression or died according to an independent review committee. The median progression-free survival, as assessed by the independent review committee, was 11.9 (10.0 to 13.8) months in the nab-TPC cohort and 7.6 (6.6 to 8.7) months in the gemcitabine plus cisplatin cohort. The hazard ratio was 0.39 (0.24 to

Table 1 | Baseline demographics and disease characteristics. Values are numbers (percentages) unless stated otherwise

Characteristic	Nab-TPC group (n=41)	GP group (n=40)	Total (n=81)
Median (IQR) age, years	47 (36-57)	48 (36-56)	48 (36-57)
Age group:			
‹50 years	25 (61)	22 (55)	47 (58)
≥50 years	16 (39)	18 (45)	34 (42)
Sex:			
Male	34 (83)	30 (75)	64 (79)
Female	7 (17)	10 (25)	17 (21)
ECOG performance status:			
0	16 (39)	17 (43)	33 (41)
1	25 (61)	23 (58)	48 (59)
Histology*:			
Non-keratinising undifferentiated (type III)	41 (100)	38 (95)	79 (98)
Non-keratinising differentiated (type II)	0 (0)	2 (5)	2 (2)
Smoking status:			
Yes	18 (44)	16 (40)	34 (42)
No	23 (56)	24 (60)	47 (58)
Disease status:			
Recurrence with distant metastases	24 (59)	28 (70)	52 (64)
Primary metastases	17 (41)	12 (30)	29 (36)
No of metastatic organs:			
1	17 (41)	16 (40)	33 (41)
2	16 (39)	15 (38)	31 (38)
≥3	8 (20)	9 (23)	17 (21)
Distant metastasis:			
Liver	26 (63)	21 (53)	47 (58)
Lung	12 (29)	18 (45)	30 (37)
Bone	15 (37)	15 (38)	30 (37)
Other	19 (46)	20 (50)	39 (48)
Previous chemotherapy:			
Induction	16 (39)	21 (53)	37 (46)
Concurrent	23 (56)	25 (63)	48 (59)
Adjuvant	4 (10)	3 (8)	7 (9)
Baseline plasma EBV DNA:			
‹2000 copies/mL	17 (41)	14 (35)	31 (38)
≥2000 copies/mL	24 (59)	26 (65)	50 (62)

EBV=Epstein-Barr virus; ECOG=Eastern Cooperative Oncology Group; GP=gemcitabine and cisplatin; IQR=interquartile range; Nab-TPC=nab-paclitaxel, cisplatin, and capecitabine.
*Categorised according to World Health Organization Classification of Tumors.

0.65; P<0.001) (supplementary figure D). Sixteen deaths were reported, with eight (20.0%) deaths in the gemcitabine plus cisplatin cohort and eight (20%) deaths in the nab-TPC cohort. The overall survival data were still immature for both cohorts at the time of analysis.

Tumour responses, as assessed by the independent review committee during the interim analysis, are outlined in supplementary table E. We observed complete responses in five (12%) patients in the nab-TPC cohort and four (10%) patients in the gemcitabine plus cisplatin cohort, as well as partial responses in 29 (71%) patients in the nab-TPC cohort and 21 (53%) patients in the gemcitabine plus cisplatin cohort. The nab-TPC cohort had a significantly higher objective response rate than the gemcitabine plus cisplatin cohort (34/41 (83%) *v* 25/40 (63%); P=0.05). Among responders, the median duration of response was notably longer in the nab-TPC cohort (10.8 (8.8 to 12.8) months) than in the gemcitabine plus cisplatin cohort (6.9 (5.5 to 8.2) months), with a hazard ratio of 0.42 (0.22 to 0.81; P=0.009) (fig 2). However, the disease control rate was similar in the two treatment cohorts (1/41 (98%) *v* 3/40 (92.5%); P=0.36). Tumour burden and response in patients with baseline positive or negative plasma EBV DNA levels are shown in supplementary table C.

Safety

Table 2 shows the treatment related adverse events that occurred in ≥5% of patients. The most common adverse events were haematological and gastrointestinal. However, the overall incidence of grade 3 or 4 adverse events was low in both of cohorts (table 2). Treatment related grade 3 or 4 adverse events that differed significantly between the nab-TPC and gemcitabine plus cisplatin cohorts were leucopenia (10% *v* 33%); P=0.02), neutropenia (15% *v* 40%; P=0.01), and anaemia (2% *v* 20%; P=0.01). The rate of discontinuation due to drug related adverse events was 2% (1/41) in the nab-TPC cohort and 3% (1/40) in the gemcitabine plus cisplatin cohort. Dose reductions occurred in five (12%) patients in the nab-TPC cohort and 10 (25%) patients in the gemcitabine plus cisplatin cohort. No treatment related deaths were reported during the trial.

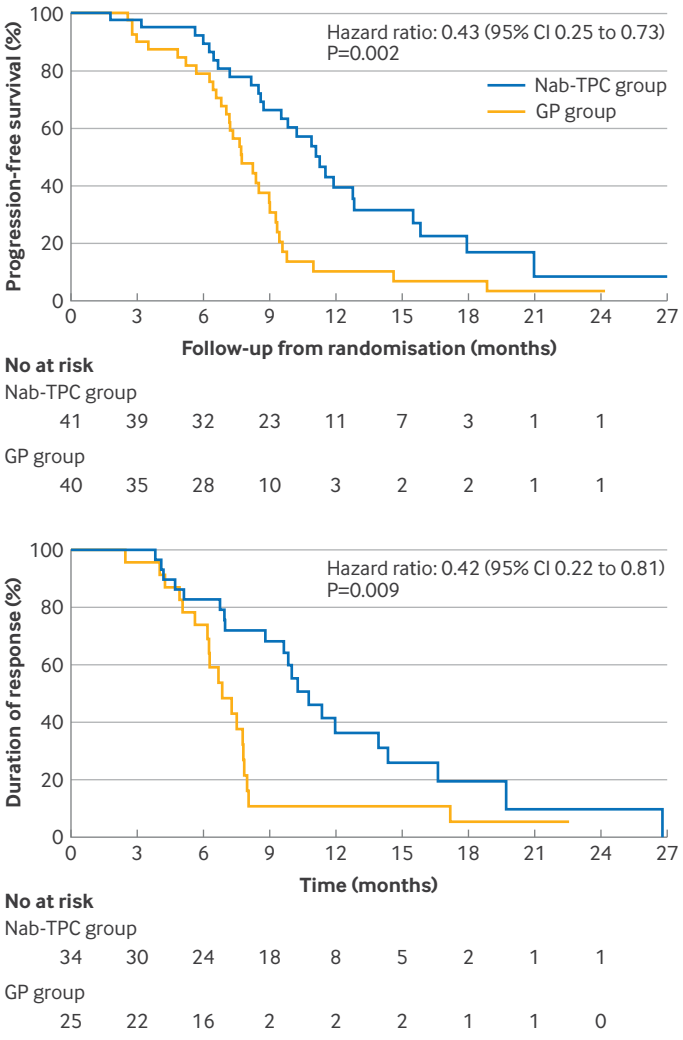


Fig 2 | Kaplan-Meier plots of progression-free survival (top) and duration of response (bottom) assessed by independent review of images from randomly assigned patients. CI=confidence interval; GP=gemcitabine and cisplatin; Nab-TPC=nab-paclitaxel, cisplatin, and capecitabine

Discussion

The nab-TPC regimen showed a substantial extension in progression-free survival compared with the conventional gemcitabine plus cisplatin chemotherapy regimen. This difference reached statistical significance in the pre-planned interim analysis focused on progression-free survival. The adverse events associated with the nab-TPC regimen were found to be manageable. Notably, this study represents the first prospective, multicentre, randomised clinical trial illustrating the progression-free survival benefits and objective response rate of the nab-TPC regimen in the first line treatment of recurrent or metastatic nasopharyngeal carcinoma.

Comparison with other studies

In a landmark phase 3 trial conducted in 2016 in patients with recurrent or metastatic nasopharyngeal carcinoma, gemcitabine plus cisplatin showed superior progression-free survival compared with a fluorouracil plus cisplatin regimen, thereby establishing gemcitabine plus cisplatin as a preferred first line regimen option.[6 7] However, the study found a median progression-free survival of seven months with the gemcitabine plus cisplatin regimen. In our recently reported prospective phase 3 trial, using capecitabine maintenance following paclitaxel, cisplatin, and capecitabine (TPC) chemotherapy for disease control in metastatic nasopharyngeal carcinoma, the median progression-free survival extended to 35.5 months. Interestingly, we noticed that the response rate with TPC was higher than for the gemcitabine plus cisplatin regimen before capecitabine maintenance was initiated (74% *v* 64%), strongly indicating superior tumour control efficacy with TPC chemotherapy.[10] Nevertheless, nab-paclitaxel has shown a higher complete remission rate than conventional taxanes, with anaphylaxis being rare.[14] Owing to the promising antitumour effects of the nab-TPC regimen, we conducted a controlled, randomised, phase 3 trial

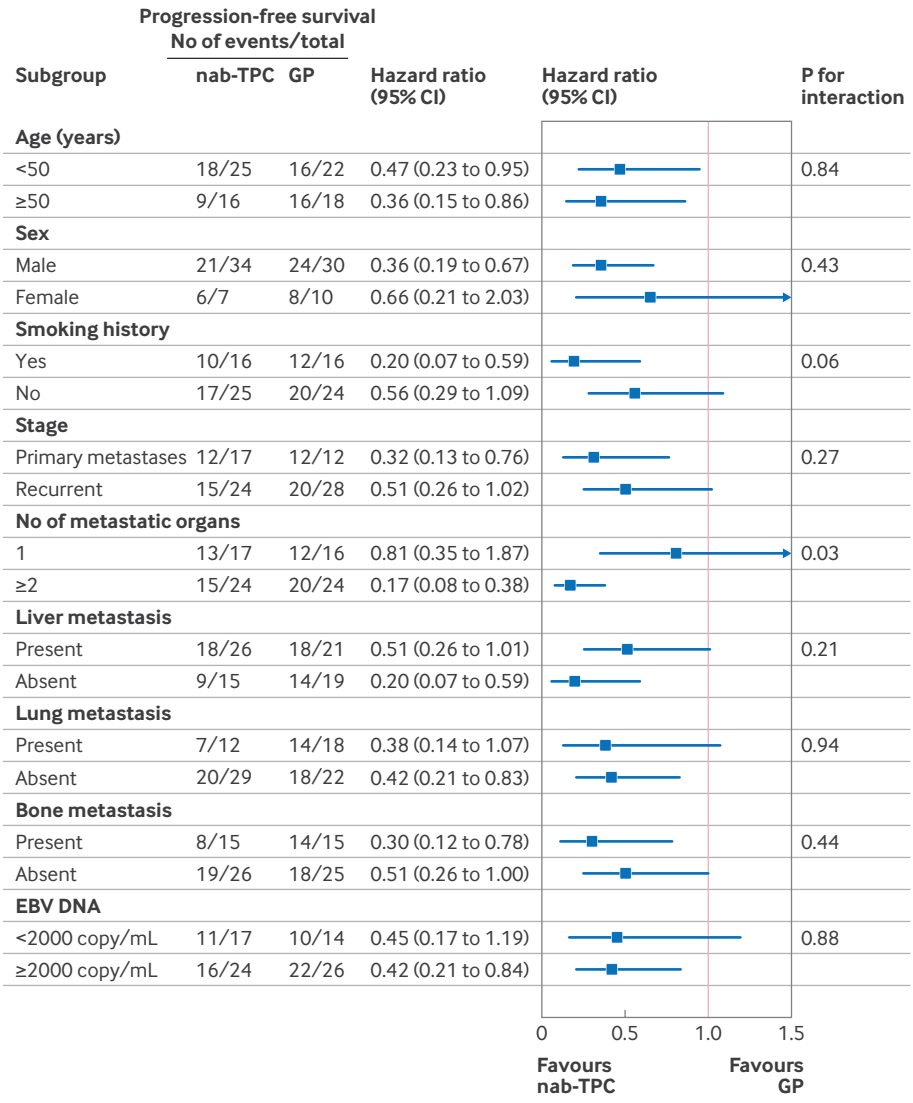


Fig 3 | Hazard ratio of progression-free survival (nab-TPC over GP) in subgroups according to baseline characteristics. CI=confidence interval; EBV-Epstein-Barr virus; GP=gemcitabine and cisplatin; nab-TPC=paclitaxel, cisplatin, and capecitabine

to assess its antitumour efficacy compared with a standard gemcitabine plus cisplatin regimen for recurrent or metastatic nasopharyngeal carcinoma.

The median progression-free survival was 7.7 months for the gemcitabine plus cisplatin group in this study, which was similar to that reported in the previous studies in recurrent or metastatic nasopharyngeal carcinoma.[9 15] Notably, the nab-TPC treatment cohort showed a significant improvement, with a median increase of 3.6 months in progression-free survival among the intention-to-treat population. This improvement represents a 57% reduction in immediate risk of disease progression or mortality compared with the gemcitabine plus cisplatin treatment group. We note that median progression-free survival of nab-TPC regimen in this trial was shorter than the previously reported result. Several reasons contributed to this difference. First of all, the results from a post hoc subgroup analysis showed that patients without liver metastasis would more likely to achieve improved survival through capecitabine maintenance therapy.[10] More than half of patients (63.4%) enrolled in this trial had liver metastasis, compared with 38.5% of patients in the previous study.[10 16] Secondly, and importantly, the method of calculating progression-free survival is different. In this trial, we assessed it from randomisation (before chemotherapy started) to disease progression, whereas in the previous study it was counted from the time of randomisation (after achievement of disease control with the TPC regimen) to disease progression. In addition, patients who progressed during TPC treatment were excluded from capecitabine maintenance therapy in the previous study.

In our study, the nab-TPC regimen achieved a significant 20% improvement in objective response

Table 2 | Common drug related adverse events. Values are numbers (percentages) unless stated otherwise

Adverse event	Nab-TPC group (n=41)				GP group (n=40)				P for difference in all grades	P for difference in 3-4 grades
	Any grade	Grade 1-2	Grade 3	Grade 4	Any grade	Grade 1-2	Grade 3	Grade 4		
Haematological toxicities										
Leukopenia	17 (41)	13 (32)	4 (10)	0	30 (75)	17 (43)	11 (28)	2 (5)	0.02	0.02
Neutropenia	13 (32)	7 (17)	5 (12)	1 (2)	31 (78)	15 (38)	12 (30)	4 (10)	0.001	0.01
Anaemia	17 (41)	16 (39)	1 (2)	0	30 (75)	21 (55)	8 (20)	0	0.001	0.01
Thrombocytopenia	3 (7)	3 (7)	0	0	16 (40)	13 (33)	1 (3)	2 (5)	0.008	0.12
Non-haematological toxicities										
ALT increased	12 (29)	11 (27)	0	1* (2)	6 (15)	6 (15)	0	0	0.37	1.00
AST increased	11 (27)	10 (24)	0	1* (2)	5 (13)	5 (13)	0	0	0.37	1.00
Blood bilirubin increased	9 (22)	9 (22)	0	0	3 (8)	3 (8)	0	0	0.16	1.00
Blood creatinine increased	16 (39)	16 (39)	0	0	15 (38)	15 (38)	0	0	0.30	1.00
Decreased appetite	19 (46)	19 (46)	0	0	26 (65)	26 (65)	0	0	0.14	1.00
Hand-foot syndrome	18 (44)	14 (34)	3 (7)	1 (2)	2 (5)	2 (5)	0	0	0.001	0.12
Fatigue	8 (20)	7 (17)	1 (2)	0	7 (18)	5 (13)	2 (5)	0	0.65	0.62
Nausea	10 (24)	10 (24)	0	0	13 (33)	11 (28)	2 (5)	0	0.51	0.24
Vomiting	2 (5)	2 (5)	0	0	5 (13)	4 (10)	1 (3)	0	0.21	1.00
Mucosal inflammation	6 (15)	5 (12)	1 (2)	0	2 (5)	2 (5)	0	0	0.41	1.00

Safety analysis included all patients who were given at least one dose of investigational drug. No instances of grade 5 drug related adverse events were observed throughout study period.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; Nab-TPC=nab-paclitaxel, cisplatin, and capecitabine; GP=gemcitabine and cisplatin.
*Viral hepatitis; patient's transaminase was normal after antiviral treatment.

rate compared with the gemcitabine plus cisplatin group during the initial phase of induction chemotherapy in patients with recurrent or metastatic nasopharyngeal carcinoma (82.9% *v* 62.5%; P=0.05). Thus, this nab-TPC regimen represents an important option for patients in need of clinically meaningful tumour shrinkage. The objective response is commonly regarded as an independent predictor of survival in patients with solid tumours and may serve as a potential indicator for overall survival and progression-free survival. Meanwhile, objective response rate is strongly correlated with progression-free survival in metastatic nasopharyngeal carcinoma.[17 18] Our data are consistent with previous findings regarding the association between objective response rate and progression-free survival. Furthermore, we observed that the progression-free survival curve in the two groups started to separate at the end of the induction chemotherapy phase (fig 2), indicating the superior efficacy of nab-TPC versus the gemcitabine plus cisplatin regimen even in the induction phase. In addition, the significantly improved duration of response was also observed in the nab-TPC group (median duration of response 10.8 *v* 6.9 months; P=0.009). Likewise, as part of the nab-TPC regimen, maintenance capecitabine therapy may also play a role in improving progression-free survival. These results suggest that the nab-TPC regimen possesses more potent and enduring anticancer effects than the gemcitabine plus cisplatin regimen and could be considered as a front line treatment option for patients with recurrent or metastatic nasopharyngeal carcinoma.

Recently, three phase 3 trials reported a significant improvement in progression-free survival for gemcitabine and cisplatin plus programmed cell death protein 1 inhibitors compared with gemcitabine and cisplatin alone.[9 15 19] These findings suggest that the combination of programmed cell death protein 1 inhibitors with gemcitabine plus cisplatin has emerged as the new standard treatment for patients with recurrent or metastatic nasopharyngeal carcinoma in the front line setting. Furthermore, investigating whether the use of nab-TPC as chemotherapy backbone, combined with programmed cell death protein 1 inhibitors, improves efficacy compared with gemcitabine plus cisplatin with programmed cell death protein 1 inhibitors would be worthwhile

The adverse events profiles of nab-TPC and gemcitabine plus cisplatin in this trial were as expected. No new toxicity signals were noted during the trial. All the adverse events were generally manageable. Treatment related haematological adverse events were more frequent with the gemcitabine plus cisplatin regimen, whereas hand-foot syndrome was associated with nab-TPC regimen. However, the observed rate of hand-foot syndrome is comparable to that reported in previous clinical trials.[10] The proportion of patients discontinuing the study drugs was similar between the two cohorts.

Limitations of study

This trial has some inevitable limitations. Firstly, as all participants were sourced from endemic areas in China where non-keratinising nasopharyngeal carcinoma comprises more than 95% of cases, whether the findings can be extrapolated to non-endemic regions without further validation remains uncertain. Secondly, although the trial has achieved its primary endpoint of progression-free survival, the overall survival data have not yet fully matured. A meta-analysis of individual patient data suggested that progression-free survival was strongly correlated with overall survival in locoregional nasopharyngeal carcinoma.[20] However, measurement of overall survival is potentially diluted by administration of crossover treatment in our study

(29% of patients in the nab-TPC group and 30% of patients in the gemcitabine plus cisplatin group). Furthermore, with an increasing number of treatment options for recurrent or metastatic nasopharyngeal carcinoma and considering that regimens containing programmed cell death protein 1 inhibitor are effective in subsequent treatment, whether the same correlation exists is unclear.[21] Further follow-up is needed to ascertain any potential benefit in overall survival. Thirdly, a thorough analysis of potential predictive biomarkers is essential to identify patients who may derive benefit from the nab-TPC regimen as a first line treatment.

Conclusion

In summary, our findings show, for the first time, that the nab-TPC regimen offers a statistically significant enhancement in progression-free survival compared with the current standard-of-care gemcitabine plus cisplatin regimen in recurrent or metastatic nasopharyngeal carcinoma as a first line treatment. The nab-TPC regimen has a manageable safety profile. These results advocate for the inclusion of the nab-TPC regimen as a standard treatment option for patients with recurrent or metastatic nasopharyngeal carcinoma and propose its suitability as a control arm in future randomised clinical trials.

AUTHOR AFFILIATIONS

[1]Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of NPC Diagnosis and Therapy, Guangzhou, China

[2]Department of Oncology, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Medical Research Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

[3]Clinical Research Design Division, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Medical Research Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

[4]Southern University of Science and Technology, Shenzhen, China

[5]Department of Oncology, Maoming People's Hospital, Maoming, China

[6]Department of Radiation Oncology, Wuzhou Red Cross Hospital, Wuzhou, China

[7]Department of Medical Imaging, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of NPC Diagnosis and Therapy, Guangzhou, China

[8]Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[9]Medical Research Center, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Medical Research Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

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Contributors: YQX, HRY, and CX were responsible for the study concept and design. GYL, YFY, YFJ, WXX, TSG, YSH, YML, YTH, JFL, JHL, CLC, GJC, HL, NL, WXB, WZL, SHD, and QL were involved in the acquisition, analysis, or interpretation of data. GYL, YFY, YFJ, GJC, WXX, YSH, TSG, CX, HRY, and YQX drafted the manuscript. GYL, YFY, YFJ, CX, HRY, and YQX critically revised the manuscript for important intellectual content. GYL, YFY, and GJC did the statistical analysis. YQX, GYL, and WXX obtained funding. YQZ provided administrative, technical, or material support. YQX, HRY, and CX supervised the study. GYL, YFY, YFJ, GJC, WXX, YSH, and TSG contributed equally to this study. YQX, HRY, and CX are joint senior authors and are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20190198) and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

Data sharing: Taking into account patient privacy and relevant regulations in China, we have decided against making the database publicly accessible to all. However, the raw database will be securely deposited on the Research Data Deposit public platform (www.researchdata.org.cn). Researchers interested in using the raw data for scientific research purposes may request access through our corresponding author and database administrator.

Transparency: The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results were communicated to the participating sites. The results of the study may be communicated to study participants who express an interest at the time of clinic visits. Concurrent outreach to the public will be through the media.

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1 Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *Lancet* 2019;394:64-80. doi:10.1016/S0140-6736(19)30956-0
2 Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-49. doi:10.3322/caac.21660
3 Zhang Y, Chen L, Hu GQ, et al. Final Overall Survival Analysis of Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma: A Multicenter, Randomized Phase III Trial. *J Clin Oncol* 2022;40:2420-5. doi:10.1200/JCO.22.00327
4 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* 2021;398:303-13. doi:10.1016/S0140-6736(21)01123-5
5 Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol* 2016;17:1509-20. doi:10.1016/S1470-2045(16)30410-7
6 Hong S, Zhang Y, Yu G, et al. 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. *J Clin Oncol* 2021;39:3273-82. doi:10.1200/JCO.21.00396

7 Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2016;388:1883-92. doi:10.1016/S0140-6736(16)31388-5
8 Caudell JJ, Gillison ML, Maghami E, et al. NCCN Guidelines® Insights: Head and Neck Cancers, Version 1.2022. *J Natl Compr Canc Netw* 2022;20:224-34. doi:10.6004/jnccn.2022.0016
9 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* 2021;27:1536-43. doi:10.1038/s41591-021-01444-0
10 Liu GY, Li WZ, Wang DS, et al. Effect of Capecitabine Maintenance Therapy Plus Best Supportive Care vs Best Supportive Care Alone on Progression-Free Survival Among Patients With Newly Diagnosed Metastatic Nasopharyngeal Carcinoma Who Had Received Induction Chemotherapy: A Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2022;8:553-61. doi:10.1001/jamaoncol.2021.7366
11 Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005;23:7794-803. doi:10.1200/JCO.2005.04.937
12 Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-62. doi:10.1200/JCO.2011.39.5848
13 Huang Y, Liang W, Yang Y, et al. Phase I/II dose-finding study of nanoparticle albumin-bound paclitaxel (nab®-Paclitaxel) plus Cisplatin as Treatment for Metastatic Nasopharyngeal Carcinoma. *BMC Cancer* 2016;16:464. doi:10.1186/s12885-016-2517-5
14 Lu H, Zha S, Zhang W, et al. A systematic review and meta-analysis of nab-paclitaxel mono-chemotherapy for metastatic breast cancer. *BMC Cancer* 2021;21:830. doi:10.1186/s12885-021-08441-z
15 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* 2021;22:1162-74. doi:10.1016/S1470-2045(21)00302-8
16 Liu GY, Li WZ, Xiang YQ. Capecitabine Maintenance in Metastatic Nasopharyngeal Carcinoma-Reply. *JAMA Oncol* 2022;8:1224-5. doi:10.1001/jamaoncol.2022.2068
17 Liu GY, Li WZ, Peng KQ, et al. Prognostic value of early radiological response to first-line platinum-containing chemotherapy in patients with metastatic nasopharyngeal carcinoma. *Cancer Med* 2020;9:920-30. doi:10.1002/cam4.2751
18 Lencioni R, Montal R, Torres F, et al. Objective response by mRECIST as a predictor and potential surrogate end-point of overall survival in advanced HCC. *J Hepatol* 2017;66:1166-72. doi:10.1016/j.jhep.2017.01.012
19 Yang Y, Pan J, Wang H, et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: A multicenter phase 3 trial (RATIONALE-309). *Cancer Cell* 2023;41:1061-1072.e4. doi:10.1016/j.ccell.2023.04.014
20 Rotolo F, Pignon JP, Bourhis J, et al, MAC-NPC Collaborative Group. Surrogate End Points for Overall Survival in Loco-Regionally Advanced Nasopharyngeal Carcinoma: An Individual Patient Data Meta-analysis. *J Natl Cancer Inst* 2017;109:djw239. doi:10.1093/jnci/djw239
21 Hsu C, Lee SH, Ejadi S, et al. Safety and Antitumor Activity of Pembrolizumab in Patients With Programmed Death-Ligand 1-Positive Nasopharyngeal Carcinoma: Results of the KEYNOTE-028 Study. *J Clin Oncol* 2017;35:4050-6. doi:10.1200/JCO.2017.73.3675

Web appendix: Supplementary tables and figures
Web appendix: Trial protocol
Web appendix: Statistical code