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# Adjunctive PD-1 inhibitor *versus* standard chemotherapy in recurrent or metastatic nasopharyngeal carcinoma: a systematic review and meta-analysis

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## Abstract

**Objective:** To investigate whether Adjunctive PD-1 inhibitors have improved clinical outcomes compared to chemotherapy alone in platinum-pretreated and platinum-naive recurrent or metastatic nasopharyngeal carcinoma (R/M NPCA).

**Methods:** The study involved a literature search from PubMed, Cochrane CENTRAL, and Google Scholar for randomized clinical trials (RCTs) on the use of PD-1 inhibitors *versus* chemotherapy alone in patients with R/M NPCA. Bias was assessed using Cochrane collaboration's risk of bias tool. Overall Survival (OS) was examined as the primary endpoint. Secondary endpoints were Progression-Free Survival (PFS), Objective Response Rate, Disease Control Rate (DCR), Duration of Response, and Serious/Grade  $\geq 3$  Adverse Events. Outcomes were measured with either Mean Difference, Risk ratio (RR), or Hazard ratios (HRs) at 95% confidence interval.

**Results:** Four RCTs were included in the meta-analysis and systematic review. OS for the monotherapy subgroup was a HR of 0.87 [0.67, 1.13] ( $p=0.30$ ) while the combination subgroup had 0.64 [0.45, 0.90] ( $p=0.01$ ). The monotherapy subgroup exhibited significantly worse outcomes in PFS (HR 1.31 [1.01, 1.68]) ( $p=0.04$ ) and DCR (RR 1.52 [1.12, 2.05]) ( $p=0.007$ ) but no significant difference in other outcomes. For combination therapy, a statistically significant benefit can be seen in all outcomes except DCR (RR 0.62 [0.38, 1.01]) ( $p=0.06$ ) which was a non-significant benefit favoring PD-1 inhibitors.

**Conclusion:** Combination PD-1 inhibitor + chemotherapy followed by maintenance PD-1 inhibitor therapy is superior to chemotherapy alone in the first-line treatment of R/M NPCA, implying a potential benefit with the use of PD-1 inhibitors + chemotherapy with maintenance PD-1 inhibitors as first-line in R/M NPCA compared to standard chemotherapy alone.

**Keywords:** anti-PD-1, checkpoint inhibitor, chemotherapy, metastasis, nasopharyngeal carcinoma

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## Introduction

Nasopharyngeal carcinoma (NPCA) is a malignant neoplasm developing from the epithelial lining of the nasopharynx and commonly associated with Epstein-Barr virus (EBV) infection. It is notable as one of the malignancies with a known ethnic predisposition, arising primarily from

people of Chinese descent. Aligning with this, its worldwide distribution in 2018 shows China as occupying an age-standardized incidence rate of 60,558 (47.7%) cases out of 100,000.<sup>1</sup> This was closely followed by Southeast Asia (SEA) with an age-standardized incidence rate of 29,317 (29.3%) cases out of 100,000.<sup>1</sup> This could easily

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be explained by the proximity of SEA to China, leading to a likely Chinese genetic diaspora onto these regions.

It is speculated that the Human Leukocyte Antigen (HLA) gene and the Cytochrome P450 2A6 (CYP2A6) genes are likely culprits for the predisposition of Chinese individuals and Southeast Asians to developing NPCA. The HLA class II gene, HLA-A\*0207, was found to be carried by south Chinese populations at a significantly higher rate than in Caucasians.<sup>2,3</sup> This relates to EBV as HLA class II receptors are utilized for viral penetration after the viral glycoprotein, gp42, binds to HLA class II on the cell surface of B cells.<sup>4</sup> CYP2A6 polymorphisms were similarly found to be associated with NPCA according to a case-control study done in the National Cancer Institute of Thailand. CYP2A6 polymorphisms cause carcinogen accumulation by activating aflatoxins and nitrosamines into their ultimate form carcinogens that ultimately lead to DNA damage. It is also involved with the metabolization of nicotine, possibly predisposing to a cyclical behavior of addiction that could further expose an individual to nitrosamines from smoking.<sup>5</sup>

NPCA is highly sensitive to chemoradiation which changed its 5 years overall survival (OS) from 25 to 40% to approximately 70% in recent years.<sup>6</sup> For those with untreated recurrent or metastatic (R/M) NPCA, current studies support the efficacy of platinum-based doublet chemotherapy as the recommended treatment.<sup>7-9</sup> However, current standard of therapy often leads to a median survival rate of no more than 1 year at most in those with distant metastases.<sup>10,11</sup> Thus, studies exploring alternative treatment modalities for a possibility of providing better outcomes are warranted.

Programmed cell death protein 1 (PD-1) inhibitors have been extensively studied in other forms of malignant neoplasms, including other head and neck cancers (HNCs), showing very optimistic outcomes in their use. The phase 3 trial from Ferris *et al.*<sup>12</sup> on nivolumab use in recurrent and metastatic HNC, except NPCA, showed that OS benefit was significantly longer with nivolumab than with standard therapy [hazard ratio (HR), 0.70; 97.73% confidence interval (CI), 0.51–0.96;  $p=0.01$ ].<sup>12</sup> Similarly, the phase 3 study by Cohen *et al.*<sup>13</sup> on an identical population showed a significant benefit with pembrolizumab over standard therapy in OS [HR, 0.80 (0.65–0.98);  $p=0.016$ ].<sup>13</sup> PD-1 inhibitors are currently

accepted as a standard of treatment in non-small cell lung cancer (NSCLC) with no driver mutations expressing PD-L1 levels of  $\geq 50\%$  while becoming an essential component of therapy alongside chemotherapy in those with PD-L1 levels of  $< 50\%$ .<sup>14</sup>

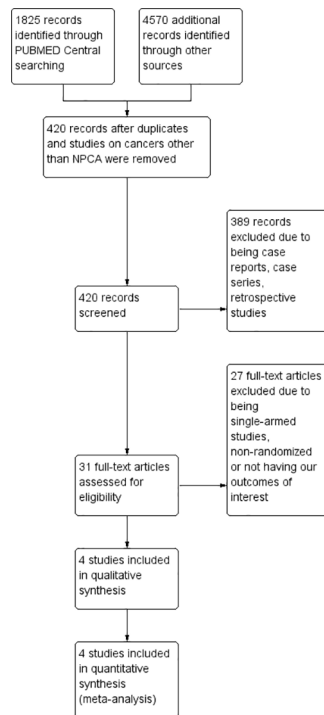
PD-1 is a surface receptor that has an important part in regulating t-cell function. It is expressed in active T cells, B cells, activated monocytes, and dendritic cells and acts as a negative regulator that helps induce self-tolerance.<sup>15</sup> When stimulated, PD-1 inhibits early activation events of involved cells in the presence of the co-stimulatory signals: CD28 and IL-2. Both CD28 and IL-2 promote an antiapoptotic effect as it affects PD-1. Consequently, withdrawal of these cytokines leads to cell death.<sup>15</sup> With regards to cancers, the most important ligand for PD-1 is the Programmed death-ligand 1 (PD-L1) protein. PD-L1 is usually expressed by tumor-associated antigen presenting cells including dendritic cells, macrophages, fibroblasts, and T cells.<sup>16</sup> It is positively regulated by interferon- $\gamma$  which is induced in effector t-cells by the presence of tumor cells.<sup>16</sup> When bound to PD-1, PD-L1 inhibits the process of apoptosis that leads to uncontrolled cell growth. Hence the reason why drugs that inhibit the binding of PD-1 to PD-L1 would negatively impact the proliferation of tumor cells. This relationship between PD-1, PD-L1, their chemical regulators, and the association of EBV infection with an increased PD-L1 expression all help explain the role of PD-1/PD-L1 interaction in the growth of NPCA and the rationale behind the use of PD-1 inhibitors as a treatment for malignancy.<sup>17</sup>

A meta-analysis would benefit the limited trials currently available by increasing the total power of the studies through pooling together and synthesizing their results. Because of this, we have decided to investigate the efficacy and safety of PD-1 inhibitors as a therapeutic approach for R/M NPCA by doing a meta-analysis.

## Methodology

### Eligibility criteria

Randomized controlled trials comparing the use of PD-1 inhibitors, with or without chemotherapy, compared to chemotherapy alone in R/M NPCA among adult patients were included in the study. A control group composed of patients



**Figure 1.** Flow diagram of literature search and study selection based on preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P) recommendation. NPCA, nasopharyngeal carcinoma.

diagnosed with NPCA and treated with chemotherapy must be present. The studies included must have a sample population of only adult patients with histologic diagnosis of NPCA. Retrospective studies, case reports, case series, single-armed, and non-randomized studies were excluded from the meta-analysis. Pediatric patients were also excluded given innate differences in physiology. Furthermore, the studies included must also look at the OS, Progression-Free Survival (PFS), Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR), and must provide either the actual counts or HRs. Adverse Effects (AEs) were also included but must be classified as Serious or Grade  $\geq 3$ .

#### Search methods for identification of studies

The search was done according to the PRISMA-P guidelines and wasn't restricted by language, date, publication status, or any other trial characteristics. The following electronic databases were utilized for the search: PubMed Central as the primary database. Cochrane CENTRAL and

Google Scholar were used as secondary database. Specific search keywords and MeSH terms used were: 'nasopharyngeal carcinoma OR npca', 'recurrent OR metastatic', 'PD-1', 'camrelizumab OR toripalimab OR pembrolizumab OR spartalizumab OR nivolumab OR checkpoint inhibitor OR anti PD', 'chemotherapy' and 'clinical trial OR RCT OR randomized clinical trial OR randomized controlled trial OR randomized control trial' to search for relevant studies. The PICO question was 'Are PD-1 inhibitors, with or without chemotherapy, superior to standard chemotherapy regimens alone in patients with metastatic or recurrent NPCA?'. References within the primary selected studies reviewed in the full text were screened as well as gray literature. Last search was done on 20 September 2022; 2:30:00 pm (Figure 1).

#### Selection of studies

Two authors (ETP and JAC) independently screened each title and abstract of each study. For studies with uncertainties evaluated in the title and abstract, the full text was reviewed. All screened studies were assessed for inclusion in accordance with the eligibility criteria. Disagreements were resolved by discussions between the two screening authors. A third author (SC) was consulted when a consensus could not be met.

#### Data extraction

From the included studies, data were independently extracted such as the type of study design, year of publication, country of origin, sample size and their baseline characteristics, inclusion and exclusion criteria, treatment arms, dosage, length of follow-up, and reported outcomes. From this, the eligibility criteria as well as the nature of intervention were derived.

#### Outcomes

The primary outcome measure is the OS calculated from both arms and measured in months. We define the OS as the time from randomization until death from any cause.<sup>18</sup> Secondary outcomes include PFS, ORR, DCR, DOR, and Serious or Grade  $\geq 3$  drug-related AEs. ORR is computed by adding complete response and partial response. DCR used the percentage of complete response, partial response, and stable disease. HR was used for OS and PFS measurement. Risk ratio (RR) was used for ORR, DCR, and AEs. Mean difference (MD) was used to measure DOR. All pooled

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AT Chan, et al., 2021	+	+	-	-	+	+	-
Caroline Even, et al., 2021	+	+	-	-	+	+	-
Hai-Qiang Mai, et al., 2021	+	+	+	+	+	+	-
Yunpeng Yang, et al., 2021	+	+	+	+	+	+	-

**Figure 2.** Risk of bias summary; green: low risk; red: high risk; other bias: presence of sponsorship bias due to financial support from either Merck Sharp & Dohme Corp, Novartis Pharmaceuticals Corporation, Shanghai Junshi Biosciences, or Jiangsu Hengrui Pharmaceuticals and Junshipharma.

outcomes were assessed with 95% CIs with a random-effects model.

#### Risk of bias

Two authors (ETP and JAC) independently assessed the risk of systematic errors (bias) in the included studies using the Cochrane collaboration's risk of bias tool for randomized studies.<sup>19</sup> The criteria to appraise the studies included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases were assessed (Figure 2).

#### Data synthesis

Review Manager version 5.4.1 was used for data synthesis of OS, PFS, ORR, DCR, DOR, and

Serious or Grade  $\geq 3$  drug-related AEs. Data types for OS and PFS utilized an inverse-variance model with HR as the measure of association. Meanwhile, a dichotomous analysis utilizing RR was used for ORR, DCR, and AEs. However, plotting of results for ORR and DCR was analyzed through non-events analysis to assess the amount of non-responders while events analysis was used for AE. DOR was analyzed with a continuous data model using the mean in months to plot the MD between study arms. All outcomes were assessed for significance using *p*-values and outliers with the *z*-score. Where appropriate, the median was used as a surrogate for the mean by conversion using the methods described by Hozo *et al.* (2005).<sup>20</sup> The standard of error for plotting HR was computed with the formula  $\ln(\text{HR})/z$  score or  $[\ln(\text{upper limit of CI}) - \ln(\text{lower limit of CI})]/3.92$ .<sup>19</sup> For studies with no reported HR, HR was estimated using the hazard rate obtained with the formula  $h = \ln(2)/$

Mean Survival Time.<sup>21</sup> Random effects were used for all data synthesized.

### Assessment of heterogeneity

Heterogeneity was tested by *df*, *I*<sup>2</sup>, *Chi*<sup>2</sup>, and *Tau*<sup>2</sup>. *I*<sup>2</sup> was interpreted as follows: 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity.<sup>19</sup> Subgroup analysis was used in an attempt to control for any heterogeneity.

## Results

### Search results

Around 4 out of 420 studies were included into the meta-analysis. Included studies were required to be two-armed randomized clinical trials (RCTs) measuring the difference between PD-1 inhibitors *versus* standard chemotherapy on an adult NPCA population. Retrospective studies, case reports or case series, including studies in pediatric patients, were excluded. Single-armed and non-randomized studies were also excluded from the data synthesis. PubMed, Cochrane CENTRAL, and Google Scholar were used to search for eligible studies. Studies must have also measured OS, PFS, ORR, DCR, DOR, and Serious or Grade  $\geq 3$  drug-related AEs as outcomes to be included into the meta-analysis. A flow-diagram of the search strategy can be seen in Figure 1.

All included studies were RCTs comparing the efficacy and safety of PD-1 inhibitors *versus* chemotherapy published in 2021. The studies by Chan *et al.*,<sup>22</sup> Yang *et al.*,<sup>23</sup> and Mai *et al.*<sup>24</sup> were all Phase III RCTs whereas the study by Even *et al.*<sup>25</sup> was a Phase II RCT. All three were published as original articles with the exception of Chan *et al.*<sup>22</sup> which was published as an abstract. A total of 907 participants were randomized and analyzed according to subgroups with a total of 355 in the monotherapy subgroup and 552 in the combination subgroup. In the analysis, certain distinctions were made for subgroup pairings. The studies by Chan *et al.* and Even *et al.* were categorized as the monotherapy subgroup while the studies by Yang *et al.* and Mai *et al.* were categorized as the combination therapy subgroup. Characteristics shared within the monotherapy subgroup were the use of single-agent PD-1 inhibitors, an open-label study design, and a population of platinum-pretreated R/M NPCA.

Whereas those in the combination subgroup were given combined PD-1 inhibitor + chemotherapy, had a double-blinded design, and a population of R/M NPCA undergoing first-line treatment. A cumulative subgroup analysis was not done due to inherent differences in their populations, namely whether patients were platinum pretreated or undergoing first-line therapy. A more comprehensive descriptive analysis of the individual studies can be seen in Table 1.

### Objective response rate

PD-1 monotherapy subgroup analysis showed an RR of 1.12 [0.90, 1.37] ( $p=0.31$ ). The combination subgroup showed an RR of 0.67 [0.49, 0.91] ( $p=0.01$ ) (Supplemental Figure 1).

### Disease control rate

PD-1 monotherapy subgroup showed an RR of 1.52 [1.12, 2.05] ( $p=0.007$ ). Combination therapy showed an RR of 0.62 [0.38, 1.01] ( $p=0.06$ ) (Supplemental Figure 2).

### Duration of response

PD-1 monotherapy showed an MD of 2.43 [−2.86, 7.73] ( $p=0.37$ ), revealing a non-significant benefit. The combination therapy subgroup showed a statistically significant benefit with an MD of 3.71 [2.35, 5.06] ( $p<0.001$ ) (Supplemental Figure 3).

### Safety

The monotherapy subgroup revealed an RR of 0.64 [0.30, 1.39] ( $p=0.26$ ) for Total Adverse Events (Supplemental Figure 4) While the combination subgroup showed an RR of 1.01 [0.96, 1.07] ( $p=0.65$ ) for Total Adverse Events (Supplemental Figure 5). Analysis of specific AEs showed no significant difference between treatment and control arms with the exceptions of monotherapy anemia (RR 0.13 [0.02, 0.71];  $p=0.02$ ), monotherapy neutropenia (RR 0.08 [0.01, 1.01];  $p=0.05$ ), and monotherapy diarrhea (RR 0.10 [0.01, 0.83];  $p=0.03$ ). Information on the AEs included in the data synthesis can be seen on Supplemental Table 1.

### Progression-free survival

The PFS for PD-1 monotherapy showed an HR of 1.31 [1.01, 1.68] ( $p=0.04$ ). Whereas, the

**Table 1.** Summary of study characteristics.

First author, title, year, design, location	Inclusion criteria	Exclusion criteria	Baseline characteristics	Treatment arms, dosage and length of follow-up	Outcomes
Chan <i>et al.</i> 8580 Results of KEYNOTE-122: A phase III study of pembrolizumab versus chemotherapy (chemo) for platinum-pretreated, recurrent nasopharyngeal carcinoma (NPCA) 2021	Histologically confirmed non-keratinizing differentiated NPCA or undifferentiated NPCA Metastatic disease or incurable locally recurrent disease Treatment with prior platinum therapy Tumor tissue available for PD-L1 testing Measurable disease based on RECIST 1.1 ECOG performance status of 0 or 1	Previously treated in the recurrent/metastatic setting with any one of the three standard therapies Immunodeficiency Prior anti-cancer monoclonal antibody (mAb) therapy Active autoimmune disease Active infection Human (HIV) hepatitis B or C positive Pregnant, breastfeeding, or expecting to conceive or father children Live vaccine within 30 days of planned start of study drug	Age, years (mean SD) Pembrolizumab: 50.6 (12.7) Standard treatment: 53.1 (11.2) Sex Male: 82.8% Female: 17.2% Race Asian: 95.3% Black: 0.4% White: 4.3% PD-L1 CPS $\geq$ 1. Pembrolizumab: 87 (74.4%) Chemotherapy: 73 (62.9%)	Total $n = 233$ <b>Intervention:</b> Pembrolizumab (n = 117); pembrolizumab 200 mg intravenously (IV) on day 1 of each 3-week cycle (Q3W) until progressive disease (PD) or unacceptable toxicity for a maximum of up to 35 cycles (up to approximately 2 years). <b>Control:</b> Standard doses of chemo (n = 116); capecitabine 1000 mg/m <sup>2</sup> orally (PO) twice each day (BID) on Days 1–14 of each 3-week cycle, or gemcitabine 1250 mg/m <sup>2</sup> IV on Days 1 and 8 of each 3-week cycle, or docetaxel 75 mg/m <sup>2</sup> IV on day 1 of each 3-week cycle until PD or unacceptable toxicity. <b>Follow-up:</b> up to 53 months	<b>OS</b> , median (95% CI), mo Pembrolizumab: 17.2 (11.7–22.9) Standard treatment: 15.3 (10.9–18.1) Hazard ratio (HR) (95% CI): 0.90 (0.67–1.19) $p = 0.2262$ <b>PFS</b> , median (95% CI), mo Pembrolizumab: 4.1 (2.1–5.6) Standard Treatment: 5.5 (4.0–8.1) HR (95% CI): 1.28 (0.94–1.75) $p = 0.9419$ <b>ORR</b> , % (95% CI) Pembrolizumab: 21.4% (14.3–29.9) Standard treatment: 23.3% (15.9–32.0) $p = 0.63479$ <b>DCR</b> (CR + PR + SD), % (95% CI) Pembrolizumab: 50.4% (41.0–59.8) Standard treatment: 63.8% (54.4–72.5) $p = 0.0414^*$ <b>DOR</b> , median (range), mo Pembrolizumab: 12.0 (1.7 + to 49.7 +) Standard treatment: 13.1 (2.6–49.3 +) $p = 0.7389^*$
Even <i>et al.</i> Phase II, randomized study of spartalizumab (PDR001), an anti-PD-1 antibody, versus chemotherapy in patients with R/M nasopharyngeal cancer 2021	Histologically documented non-keratinizing locally advanced R/M NPCA Resistant to platinum-based chemotherapy May have received up to two prior systemic therapies At least one measurable lesion (as per RECIST v1.1) Must be willing to undergo testing for HIV If HIV+ positive, eligible if: CD4+ count $\geq$ 300/ $\mu$ L; undetectable viral load; on HAART	Severe hypersensitivity reactions to other mAbs Autoimmune disease. Active HBV or HCV infections requiring therapy Prior PD-1- or PD-L1-directed therapy Systemic treatment with any immunosuppressive Use of any vaccines within 4 weeks of initiation of study treatment.	Age, years (range) Spartalizumab: 51 (21–74) Chemotherapy: 50 (26–78) Sex Male: 82.8% Female: 17.2% Race Asian: 87.7% White: 11.5% Black: 0.8% PD-L1 expression, percent positive tumor cells Spartalizumab: 78 (95.1%) Chemotherapy: 38 (95.0%)	Total $n = 122$ <b>Intervention:</b> Spartalizumab (n = 82); Spartalizumab administered IV at 400 mg every 4 weeks in 28-day cycles until unacceptable toxicity, PD per irRC, and/or treatment discontinuation due to patient/physician's decision <b>Control:</b> Investigator's choice chemotherapy (n = 40); chemotherapy per investigator's choice was dosed according to the drug label(s) <b>Follow-up:</b> From randomization up to maximum of 3.3 years	<b>OS</b> , median (95% CI), mo Spartalizumab: 25.2 months (95% CI, 13.1–NE) Chemotherapy: 15.5 months (95% CI, 8.3–21.3) HR = 0.615* $p = 0.138$ <b>PFS</b> , median (95% CI), mo Spartalizumab: 1.9 months (95% CI, 1.8–3.6) Chemotherapy: 6.6 months (95% CI, 3.7–9.3) HR 1.36 (95% CI, 0.87–2.12) One-sided stratified log-rank test $p = 0.915$ <b>ORR</b> , % (95% CI) Spartalizumab: 17.1% (95% CI, 9.7–27.0) Chemotherapy: 35.0% (95% CI, 20.6–51.7) $p = 0.0272^*$

(Continued)



Table 1. (Continued)

First author, title, year, design, location	Inclusion criteria	Exclusion criteria	Baseline characteristics	Treatment arms, dosage and length of follow-up	Outcomes
Mai <i>et al.</i> Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial 2021 Phase III, double-blinded, RCT International Multicenter Cohort in China, Taiwan, and Singapore	Age $\geq 18$ and $\leq 75$ years Histological/cytological confirmation of NPCA Primarily metastatic (stage IVB) or recurrent NPCA At least one measurable lesion according to RECIST version 1.1 Life expectancy $\geq 3$ months	Possible benefit from curative treatments History of severe hypersensitivity reactions to other mAbs Prior therapy with Checkpoint Inhibitors Major surgical procedure other than for diagnosis of NPCA within 28 days History of hypersensitivity to gemcitabine or cisplatin Female patients who are at pregnancy or lactation	Age, years (median, IQR) Toripalimab + GP: 46 (19–72) Placebo + GP: 51 (21–72) Sex Male: 83.04% Female: 16.96% Ethnicity Asian: 100% PDL1 positive Toripalimab + GP: 109 (75%) Placebo + GP: 109 (76%)	Total $n = 289$ <b>Intervention:</b> Toripalimab + GP ( $n = 146$ ); means of 11.5 cycles, 38.31 weeks for toripalimab; 5.1 cycles, 17.16 weeks for cisplatin; 5.3 cycles, 18.62 weeks for gemcitabine <b>Control:</b> Placebo + GP ( $n = 143$ ); means of 10.7 cycles, 35.5 weeks for placebo; 5.3 cycles, 17.22 weeks for cisplatin; 5.1 cycles, 18.59 weeks for gemcitabine <b>Follow-up:</b> Up to 24 months	<b>DCR</b> (CR + PR + SD), % (95% CI) Spartalizumab: 42.7% (95% CI, 31.8–54.1) Chemotherapy: 70.0% (95% CI, 53.5–83.4) $p = 0.0027^*$ <b>DOR</b> , median (range), mo Spartalizumab: 10.2 months (95% CI, 7.4–NE) Chemotherapy: 5.7 months (95% CI, 3.7–7.4) $p = 0.0370^*$ <b>OS</b> , median (95% CI), mo Toripalimab + GP: NE Placebo + gemcitabine + cisplatin: NE HR = 0.603 (95% CI: 0.364–0.997) $p = 0.0462$ <b>PFS</b> , median (95% CI), mo Toripalimab + GP: 11.7 months (95% CI: 11.0–NE) Placebo + GP: 8.0 months (95% CI: 7.0–9.5) HR = 0.52 (95% CI: 0.36–0.74) Two-sided $p = 0.0003$ <b>ORR</b> , % (95% CI) Toripalimab + GP: 77.4% (95% CI: 69.8–83.9) Placebo + gemcitabine + cisplatin: 66.4% (95% CI: 58.1–74.1) $p = 0.04^*$ <b>DCR</b> (CR + PR + SD), % (95% CI) Toripalimab + GP: 87.7% (95% CI: 81.2–92.5) Placebo + gemcitabine + cisplatin: 79.7% (95% CI: 72.2–86.0) $p = 0.0694^*$ <b>DOR</b> , median (range), mo Toripalimab + GP: 10.0 months (95% CI: 8.8–NE) Placebo + GP: 5.7 months (95% CI: 5.4–6.8) $p < 0.0001^*$

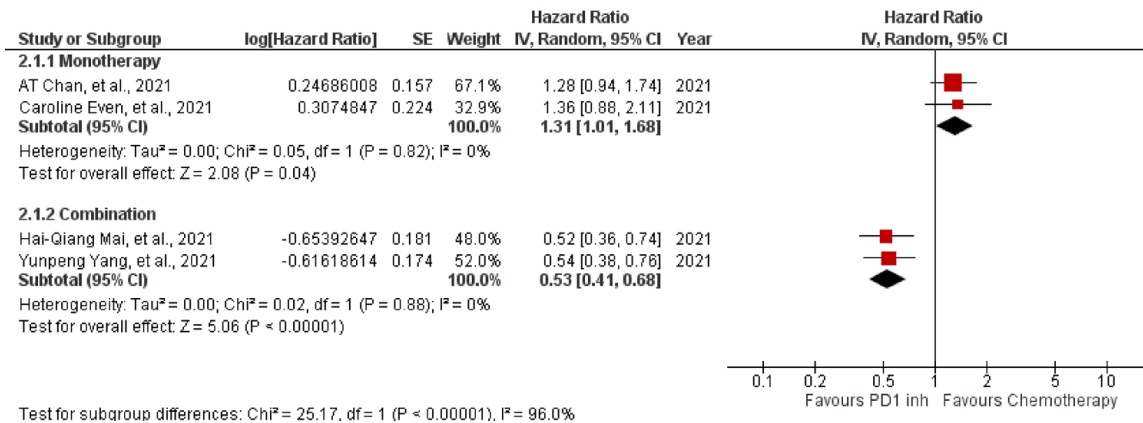
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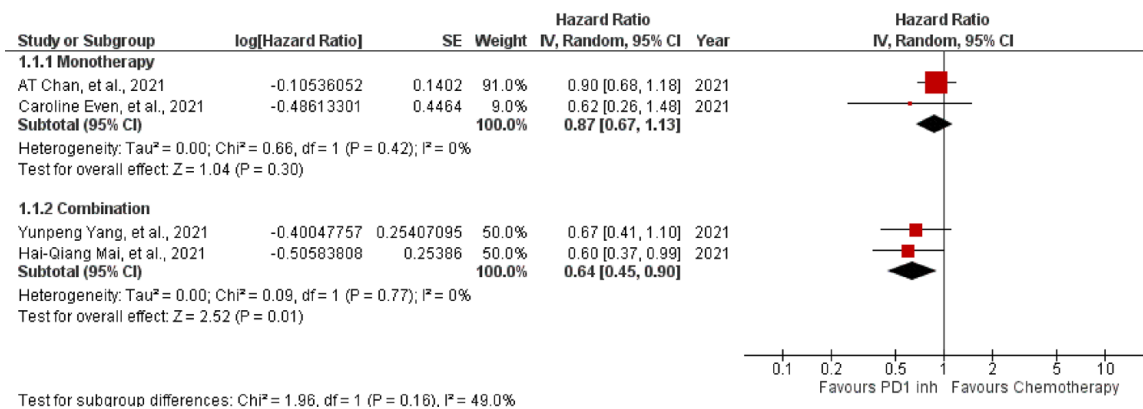
First author, title, year, design, location	Inclusion criteria	Exclusion criteria	Baseline characteristics	Treatment arms, dosage and length of follow-up	Outcomes
Yang <i>et al.</i> Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for R/M nasopharyngeal carcinoma (CAPTAIN-1st): a multicenter, randomized, double-blind, phase 3 trial Phase III, double-blinded, RCT China	Age ≥18 and ≤75 years Subjects with histopathological diagnosis of nasopharyngeal carcinoma Primarily metastatic (stage IVB) or recurrent NPCA Has not received prior systemic treatment Has an ECOG performance status of 0 or 1 Subject must have a measurable target lesion based on RECIST v1.1 Had a life expectancy of at least 12 weeks	Possible benefit from curative treatments Symptomatic CNS metastases Other malignant diseases Previous checkpoint inhibitor use Immunodeficiency History of non-infectious pneumonitis Had active hepatitis B or C infection Had active tuberculosis infection Had uncontrolled cardiac disease	Age, years (median, IQR) Camrelizumab + GP: 52 (40–58) Placebo + GP: 49 (40–56) Sex Male: 82.9% Female: 17.1% Ethnicity Asian: 100% Did not screen patients according to PD-L1 status	Total n = 263 <b>Intervention</b> Camrelizumab + GP (n = 134); camrelizumab (200 mg on day 1) administered IV, plus gemcitabine (1000 mg/m <sup>2</sup> on days 1 and 8) and cisplatin (80 mg/m <sup>2</sup> on day 1) every 3-week cycle for four to six cycles, followed by camrelizumab alone on day 1 of every 3-week cycle as maintenance therapy until radiographic progression, unacceptable toxicity, start of new anticancer treatment, investigator decision, or withdrawal of consent, whichever occurred first. <b>Control:</b> Placebo + GP (n = 129); placebo administered IV, plus gemcitabine (1000 mg/m <sup>2</sup> on days 1 and 8) and cisplatin (80 mg/m <sup>2</sup> on day 1) IV every 3-week cycle for four to six cycles, followed by placebo on day 1 of every 3-week cycle as maintenance therapy until radiographic progression, unacceptable toxicity, start of new anticancer treatment, investigator decision, or withdrawal of consent, whichever occurred first. <b>Follow-up:</b> Up to 24 months	<b>OS</b> , median (95% CI), mo Camrelizumab + GP: not reached Placebo + GP: 22.6 months (95% CI 19.2–not reached) HR = 0.67 (95% CI 0.41–1.11) p = 0.1150* <b>PFS</b> , median (95% CI), mo Camrelizumab + GP: 9.7 months (95% CI 8.3–11.4) Placebo + GP: 6.9 months (5.9–7.3) HR = 0.54 (95% CI 0.39–0.76) One-sided p = 0.0002 <b>ORR</b> , % (95% CI) Camrelizumab + GP: 87.3% (95% CI 80.5–92.4) Placebo + GP: 80.6% (95% CI 72.7–87.1) p = 0.1418* <b>DCR</b> (CR + PR + SD), % (95% CI) Camrelizumab + GP: 96.3% (95% CI 91.5–98.8) Placebo + GP: 94.6% (95% CI 89.1–97.8) p = 0.5120* <b>DOR</b> , median (range), mo Camrelizumab + GP: 8.5 (95% CI 6.9–11.1) Placebo + GP: 5.6 (95% CI 5.2–6.9) p = 0.0007*

\*Estimated value.

CNS, central nervous system; DCR, Disease Control Rate; DOR, Duration of Response; ECOG, Eastern Cooperative Oncology Group; GP, gemcitabine + cisplatin; HBC, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; irRC, immune-related response criteria; NE, not estimable; NPCA, nasopharyngeal cancer; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression-Free Survival; RECIST, response evaluation criteria in solid tumors.



**Figure 3.** Progression-free survival forest plot.  
95% CI, 95% confidence interval; IV, inverse variance; SE, standard of error.



**Figure 4.** Overall survival forest plot.  
95% CI, 95% confidence interval; IV, inverse variance; SE, standard of error.

combination subgroup showed an HR of 0.53 [0.41, 0.68] ( $p < 0.001$ ) (Figure 3).

#### Overall survival

PD-1 monotherapy revealed an HR of 0.87 [0.67, 1.13] ( $p = 0.30$ ). The combination subgroup revealed an HR of 0.64 [0.45, 0.90] ( $p = 0.01$ ) (Figure 4).

## Discussion

#### Included PD-1 inhibitors

The studies included in our data synthesis utilized four drugs within the category of PD-1 inhibitors: pembrolizumab, spartalizumab, toripalimab, and camrelizumab. PD-1 inhibitors are a form of targeted therapy that blocks PD-1/

PD-L1 interaction using humanized monoclonal IgG4 kappa anti-PD1 antibodies. Because of this, they have no cytotoxic effects unlike conventional chemotherapy. Pembrolizumab is the first FDA approved PD-1 inhibitor in the US on 4 September 2014.<sup>26</sup> It is often used in the treatment of metastatic or advanced unresectable melanoma and PD-1 positive NSCLC.<sup>27–29</sup> Spartalizumab is a drug that is currently not approved by the FDA for use outside of clinical trials with a phase 1 dose escalation study finding spartalizumab being well tolerated in patients with advanced solid tumors.<sup>30</sup> However unlike pembrolizumab, spartalizumab is usually associated with only a non-significant benefit in unresectable metastatic melanoma.<sup>31</sup> Toripalimab was approved for use in China in December 2018 for use in the treatment of unresectable or metastatic melanoma that has failed previous systemic

therapy and is generally well tolerated in Chinese patients with advanced malignancies.<sup>32,33</sup> Camrelizumab was a drug conditionally approved for the treatment of relapsed or refractory classical Hodgkin lymphoma who have received at least two previous systemic chemotherapies in May 2019 by China.<sup>34</sup> A more detailed comparison of the included drugs could be seen in supplemental Table 2.

#### *Monotherapy as second-line*

Results from our data synthesis of the monotherapy subgroup showed that PD-1 inhibitors exhibit no significant benefits with OS, DOR, and total AE. Significantly worse outcomes were seen on PFS and DCR while a non-significant result was seen in ORR. However, PD-1 monotherapy had significantly less rates of anemia, neutropenia, and diarrhea compared to chemotherapy alone. Which is congruent with the less cytotoxic effects of PD-1 inhibitors in contrast to platinum-based chemotherapy. When compared to the phase III trial by Cohen *et al.* on platinum pre-treated R/M squamous cell HNC samples, those with Combined Positive Score (CPS)  $\geq 1$  showed a significant OS benefit (0.74 [0.58, 0.93];  $p = 0.0049$ ).<sup>13</sup> While PFS, ORR, and AEs showed no significant difference between treatment and control arms. The difference in results between the pooled NPCA and HNC outcomes with PD-1 monotherapy tells us that the physiologic and genetic differences driving HNC do not equate to that of the NPCA population as the study by Cohen *et al.* analyzed R/M squamous cell HNC of the oropharynx, hypopharynx, and larynx. Supporting this is the fact that there is a notable predominance of Caucasians in the HNC samples by Cohen *et al.* which is in contrast to the majority Asian population from the monotherapy subgroup's NPCA samples. This highlights the necessity of differentiating NPCA from other HNCs. Additionally, Cohen *et al.* analyzed those with CPS  $\geq 1$  separately from those with CPS  $< 1$  whereas Chan *et al.* and Even *et al.* did not separate their analysis by CPS score. There is also a difference in the number of participants analyzed as Cohen *et al.* ( $n = 387$ ) outnumbers the monotherapy subgroup ( $n = 276$ ) in CPS  $\geq 1$  participants. These differences could be the reason as to why NPCA appears to be responding worse compared to other HNC. Overall, it appears that PD-1 inhibitor monotherapy is not superior to chemotherapy in the platinum pre-treated R/M NPCA in an Asian population.

#### *Combination therapy as first-line*

The combination subgroup showed a consistent benefit in all five outcomes with no significant difference noted in the risk of total AEs. In comparison, a recently published RCT abstract by Zhang *et al.* comparing tislelizumab + chemotherapy *versus* placebo + chemotherapy on 263 R/M NPCA patients undergoing first-line therapy is similar to our combination subgroup's population. Zhang *et al.*<sup>35</sup> found that an HR of 0.60 [0.35, 1.01] for OS, 0.50 [0.37, 0.68] for PFS, and 0.38 [0.25, 0.58] for PFS post-tislelizumab monotherapy after noted disease progression. The results from this study supports our findings despite the non-significant benefit seen in OS for the tislelizumab arm. Similarly, a meta-analysis using nine RCTs by Petrelli *et al.* on the usage of immune checkpoint inhibitors (ICI) on NSCLC shows similar results to our findings where OS, PFS, and ORR were found to be significantly in favor of ICI + chemotherapy compared to chemotherapy alone.<sup>36</sup> In contrast to our results however, Grade 3–5 AEs were noted to be significantly more frequent in the ICI arm. This could be explained by the usage of CTLA-4 and PD-L1 inhibitors where it was found that those patients given ipilimumab, a CTLA-4 inhibitor, or atezolizumab, a PD-L1 inhibitor, expressed significantly higher rates of AEs. It is also notable that Petrelli *et al.* showed a moderate to high amount of heterogeneity on all parameters measured ( $I^2 = 48\text{--}82\%$ ) which implies inconsistency in the effects of the pooled studies. Interestingly, Petrelli *et al.* also found that the magnitude of benefit was low in those with squamous histology, PD-L1 expression  $< 50\%$ , liver metastases, female sex, and never-smoking history. Making investigations into these subpopulations of patients is worth looking into for NPCA as well. Nonetheless, our findings suggest a general trend of improved outcomes with PD-1 inhibitor + chemotherapy over chemotherapy alone as a treatment modality in the first-line setting of R/M NPCA patients.

#### *Recommendations and caveats*

Although other published studies with PD-1 inhibitors in the HNC population show promising results, there is currently a severe lack of PD-1 or PD-L1 checkpoint inhibitor RCT studies on the NPCA population. Our meta-analysis suggests a very optimistic outcome with the use of combined PD-1 inhibitor + chemotherapy as a treatment modality in R/M NPCA as first-line treatment. Thus, we recommend more clinical

trials comparing this modality with standard of care to definitively conclude the existence of superiority which could potentially change the future management of this disease. Currently, there are three phase 3 trials (NCT04458909, NCT03924986, and NCT04974398) and one phase 1 trial (NCT04282070) ongoing that compares combined chemotherapy and PD-1 inhibitors with standard chemotherapy alone in R/M NPCA patients.<sup>37</sup> Another meta-analysis could be done once more RCTs on this subject are available for pooling.

According to a cost-effectiveness analysis by Zhu *et al.* toripalimab + chemotherapy associated with an incremental cost-effectiveness ratios (ICERs) of \$19,726 per quality-adjusted life-years (QALY) while camrelizumab + chemotherapy was associated with \$20,438 per QALY.<sup>38</sup> In comparison, standard chemotherapy is estimated to have a total cost of \$26,680 compared to \$48,525 and \$46,293 for toripalimab and camrelizumab + chemotherapy respectively. Despite this substantial increase in cost, the same study goes on to say that willingness-to-pay (WTP) for Chinese citizens was found to be at \$35,673 per QALY using a Markov model. Therefore, due to ICER being lower than WTP, it would appear that cost-effectiveness for PD-1 inhibitor therapy is still met despite the higher total cost of a PD-1 inhibitor + chemotherapy regimen for at least the Chinese population.

An interesting result from Even *et al.*<sup>25</sup> is their finding of a negative correlation between IFN-gamma, TIM-3, and LAG-3 status to spartalizumab response. Additionally, Huang *et al.* found that PD-1 inhibitors and PD-L1 inhibitors have differing effectiveness in HNC patients, as only a non-statistically significant result in PD-L1 inhibitor + chemotherapy combination was seen [PD-1 inhibitors (RR 1.91 [1.42, 2.56]); PD-L1 inhibitors (RR of 1.54 [0.81, 2.94]).<sup>39</sup> In comparison, a statistically significant benefit with PD-1 inhibitor + chemotherapy was seen from the clinical trials included in this meta-analysis as well as the subgroup analysis done by Huang *et al.* themselves. Therefore, the difference in efficacy between PD-L1 *versus* PD-1 inhibitors as well as further studies on IFN-gamma, TIM-3, and LAG-3 positive patients' response to PD-1 inhibitors would be worthwhile avenues to further investigate.

### Limitations

Only four eligible studies were included in our pooled data synthesis. The addition of a phase II trial with a smaller sample size decreases the total power of our pooled analysis. For similar reasons, the subjects may have also been given suboptimal drug dosing which could have led to the non-significant results seen.<sup>40</sup> The two studies included in the monotherapy subgroup were open-label, which predisposed both studies to performance and detection bias, and did not meet their primary endpoints. Of the studies included in the combination subgroup, the CAPTAIN-1st trial by Yang *et al.* and the JUPITER-02 trial by Mai *et al.* had the additional limitation of comparing their maintenance phase PD-1 inhibitor therapy with placebo instead of maintenance chemotherapy.<sup>23,24</sup> Notably however, this is still in line with current guidelines as maintenance chemotherapy is currently not recommended due to being associated with higher risks for AEs.<sup>41</sup> Approximately, only 60% are able to finish their planned maintenance chemotherapy and nearly 50% require dose reduction.<sup>41</sup> It is also worth noting that all studies were financed by pharmaceutical companies, risking sponsorship bias especially for those under an open-label design. However, third-party review committees were utilized by all included studies in an attempt to mitigate this effect.

In three out of four studies, PD-L1 was the only biomarker measured while Yang *et al.* didn't measure for PD-L1 status at all. There was also no measurement of outcomes by PD-L1 status, resulting in our data synthesis being unable to do a subgroup analysis response per PD-L1 status. Similarly, Even *et al.* was the only one who measured for IFN-gamma, TIM-3, and LAG-3 status which appeared to have shown a negative correlation for spartalizumab response in platinum-pretreated patients. However, their small sample size limits the validity of this finding and more studies are needed to verify this result. Another issue concerns the study by Chan *et al.* where the abstract and results have been published but has not yet undergone full peer-review at the time of this paper's writing. Additionally, all of the included studies had a majority EBV-positive patient sample. This indicates that the findings from our analysis is only applicable to EBV-positive patients. Lacking representation of EBV-negative patients, a relevant population of NPCA patients in non-endemic regions outside of Asia.

Finally, all studies included were RCTs which represent the best level of evidence available at the time of this article's writing. However, the presence of confounders leads to a downrating in validity based on the issues raised by all the aforementioned biases. Despite this, the consistent benefit seen in combination PD-1 inhibitors + chemotherapy subgroup in all five outcomes and lack of significant toxicity even after prolonged exposure in the PD-1 inhibitor arm's maintenance phase leads us to believe our present evidence warrants at least a GRADE certainty rating of moderate for all outcomes measured.<sup>42</sup> Meanwhile the monotherapy subgroup's outcomes could be given a low to moderate GRADE certainty rating due to the inherent limitations mentioned before.<sup>42</sup>

### Conclusion

In R/M NPCA, both PD-1 inhibitor monotherapy and combination therapy are comparable in safety to chemotherapy alone. However, PD-1 inhibitor monotherapy in platinum pre-treated R/M NPCA is not superior to chemotherapy alone as second-line treatment. Conversely, combination PD-1 inhibitor + chemotherapy as first-line treatment of R/M NPCA appears to be superior to chemotherapy alone, thereby implying a potential benefit with the use of PD-1 inhibitors + chemotherapy with maintenance PD-1 inhibitors as first-line in R/M NPCA as opposed to standard chemotherapy alone. More evidence from RCTs are needed to further validate the role of PD-1 inhibitors in the management of NPCA.

### Declarations

#### *Ethics approval and consent to participate*

Not applicable as there was no involvement of human participants, human data, or human tissue in this study outside of data from previously published materials.

#### *Consent for publication*

Not applicable as there was no involvement of human participants, human data, or human tissue in this study outside of data from previously published materials.

#### *Author contribution(s)*

**Edgar Theodore Polintan:** Conceptualization; Data curation; Formal analysis; Investigation;

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**Stephanie Krystel Canicula:** Data curation; Investigation; Methodology; Writing – original draft.

**Jesus Alfonso Catahay:** Data curation; Investigation; Methodology; Writing – original draft.

**Kevin Bryan Lo:** Formal analysis; Resources; Software; Supervision; Validation; Writing – review & editing.

**Miguel Villalona-Calero:** Resources; Supervision; Validation; Writing – review & editing.

**Herbert Ho-fung Loong:** Resources; Supervision; Validation; Writing – review & editing.

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#### *Competing interests*

The authors declare that there is no conflict of interest.

#### *Availability of data and materials*

The Revman file used to synthesize the extracted data from the included literature was submitted alongside this manuscript.

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#### **Supplemental material**

Supplemental material for this article is available online.

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