BJR

https://doi.org/10.1259/bjr.20181031

Received: 07 December 2018 | Revised: 05 May 2019 | Accepted: 11 May 2019

Cite this article as:
Peng L, Liu J-Q, Chen Y-P, Ma J. The next decade of clinical trials in locoregionally advanced nasopharyngeal carcinoma. *Br J Radiol* 2019; **92**: 20181031.

NASOPHARYNGEAL CARCINOMA SPECIAL FEATURE: REVIEW ARTICLE

The next decade of clinical trials in locoregionally advanced nasopharyngeal carcinoma

LIANG PENG, MD, JIN-QI LIU, MD, YU-PEI CHEN, MD and JUN MA, MD

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

Address correspondence to: Dr Jun Ma
E-mail: *majun2@mail.sysu.edu.cn*

The authors Yu-Pei Chen and Jun Ma contributed equally to the work.

Liang Peng and Jin-Qi Liu have contributed equally to this study and should be considered as co-first authors.

ABSTRACT:

Clinical trials are powerful weapons in the battle against nasopharyngeal carcinoma (NPC). Based on clinical trials conducted in the past two decades, concurrent chemoradiotherapy combined with adjuvant chemotherapy or induction chemotherapy has been recommended as the standard treatment for locoregionally advanced NPC in various guidelines. However, there remain shortcomings concerning current treatment modalities that should be refined in future research. In this article, we review the achievements of published clinical trials for locoregionally advanced NPC and propose future directions for subsequent clinical trials. We believe that refinement of current regimens of chemotherapy, de-intensification of treatment for specific groups of patients, developing personalized treatment based on predictors (*e.g.* applying plasma Epstein–Barr virus DNA) and investigating novel therapies, such as targeted therapy and immunotherapy, should be applied with the highest priority when designing clinical trials for locoregionally advanced NPC in the next decade.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an endemic disease prevalent in Southeast Asia and Mediterranean countries. In 2013, the annual incidence of NPC in Southern China was more than 40 000, accounting for nearly the half of the global incidence.[1,2] Radiotherapy (RT) was established as the definitive treatment for NPC because of the disease's radiosensitivity and anatomical constraints. For patients with early NPC [stage I, according to the eighth edition of American Joint Committee on Cancer (AJCC) staging system], RT alone could achieve good efficacy, and led to a 5 year overall survival (OS) rate of over 90%.[3] However, for patients with locoregionally advanced NPC (Stage II–IVA, AJCC eighth edition), RT combined with chemotherapy was recommended by the National Comprehensive Cancer Network guidelines (v. 2.2018).

In the past two decades, the most important achievements in the treatment for NPC have been the applications of intensity modulated radiotherapy (IMRT) and chemotherapy. Using this regimen, the treatment results for locoregionally advanced NPC have improved significantly.[3,4] In the era of evidence-based medicine, clinical trials, especially randomized clinical trials (RCTs), have played an important role in the fight against NPC. Clinical trials could provide high-quality evidence, guide clinical practices, and ultimately benefit patients. The chemotherapy used to treat locoregionally advanced NPC is a typical example that demonstrates how clinical trials can change guidelines. This article will review the development of treatments (mainly chemotherapy) for locoregionally advanced NPC achieved by clinical trials in the past two decades and provides future perspectives for clinical trials conducted for locoregionally advanced NPC.

ACHIEVEMENTS IN THE PAST TWO DECADES

Concurrent chemotherapy and concurrent-adjuvant chemotherapy

The landmark randomized Phase III Intergroup study 0099 (INT-0099) established the fundamental role of chemotherapy to treat locoregionally advanced NPC.[5] Compared with RT alone, concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy showed a 30% increase in the 5 year OS rate. The obvious improvements in survival induced by chemotherapy resulted in INT-0099 being closed ahead of schedule because of ethical considerations. Following INT-0099, several Phase III clinical trials were conducted in endemic areas, which also demonstrated the superiority of CCRT followed by adjuvant chemotherapy over RT alone[6–8] (Table 1). Concurrent chemotherapy and adjuvant chemotherapy were investigated at the same time; therefore, a question remained as to which kind of chemotherapy brings the most benefit. A factorial study tried to answer this question and concluded that concurrent chemotherapy could improve progression-free survival (PFS), while adjuvant chemotherapy failed to improve survival.[9] However, the limited number of patients in each arm undermined the reliability of this conclusion. Subsequently, four Phase III clinical trials were conducted to explore the absolute role of concurrent chemotherapy,[10–13] which proved that CCRT was superior to RT alone in terms of OS and PFS (Table 1). Based on the results of these clinical trials, CCRT followed by adjuvant chemotherapy or not was recommended for locoregionally advanced NPC by various guidelines.

Patients' tolerance to chemotherapy decreases during the post-RT period when patients are still recovering from acute chemoradiotherapy toxicities; therefore, only about 50–75% of patients could complete three scheduled cycles. Is adjuvant chemotherapy needed after CCRT? A Phase III clinical trial compared concurrent chemotherapy and concurrent-adjuvant chemotherapy in patients with III–IVB NPC (except T3-4N0, AJCC sixth edition).[14] The results showed no significant differences in 5 year OS (80% *vs* 83%, $p = 0.35$) and PFS (71% *vs* 75%, $p = 0.45$).[15] However, the conclusions of this study were undermined by the fact that only 63% of the patients completed the planned chemotherapy. Furthermore, a network meta-analysis was conducted to determine the role of adjuvant chemotherapy in the setting of CCRT.[16] This network meta-analysis included eight clinical trials that used CCRT, CCRT followed by adjuvant chemotherapy, and RT alone, which were compared in patients with locoregionally advanced NPC. No significant differences in OS, distant metastasis-free survival (DMFS), or locoregional relapse-free survival (LRFS) were found between CCRT followed by adjuvant chemotherapy and CCRT alone [OS: hazard ratio (HR) = 0.86, 95% credible interval (CrI) = 0.60–1.16; DMFS: HR = 0.86, 95% CrI = 0.62–1.16; LRFS: HR = 0.72, 95% CrI = 0.43–1.15]. In another individual patient data (IPD) network meta-analysis, adjuvant chemotherapy additional to CCRT showed a tendency to improve OS (HR = 0.85, 95% CrI = 0.68–1.05) and PFS (HR = 0.81, 95% CrI = 0.66–0.98).[17] Thus, the role of adjuvant chemotherapy in locoregionally advanced NPC remains uncertain, and the heterogeneity of the patients may account for this uncertainty.

Induction chemotherapy

The rationality of induction chemotherapy lies in its better tolerance and allowance for further chemotherapy, thus increasing the effectiveness in eradicating micro-metastasis. In addition, induction chemotherapy could shrink the tumor volume to provide better protection for vital organs, such as the brainstem. To date, several clinical trials have investigated the efficiency of induction chemotherapy additional to CCRT (Table 2). Hui et al conducted a Phase II study, and found that induction chemotherapy of docetaxel plus cisplatin followed by CCRT could significantly improve OS [HR = 0.24, 95% confidence interval (CI) (0.078–0.73)] compared with CCRT alone.[18] Based on results of this trial, induction chemotherapy followed by CCRT became a level three recommendation for locoregionally advanced NPC in the NCCN guidelines (v. 2012). Subsequently, clinical trials conducted by Fountzilas et al[18] and Tan et al[19] both reported results that induction chemotherapy followed by CCRT had no statistically significant effect on OS or PFS compared with CCRT alone. Clinical trials conducted by Sun et al,[20] Cao et al,[21] Frikha et al,[22] and Hong et al[23] reported statistically significant effects of induction chemotherapy additional to CCRT on either OS or PFS or both. Considering the controversial results of clinical trials, an IPD pooled analysis recruiting four clinical trials that were conducted in endemic areas was conducted,[24] which confirmed that the addition of induction chemotherapy to CCRT could improve the 5 year OS (HR = 0.75, 95% CI = 0.57–0.99) mainly through the improvement of distant metastasis (HR = 0.68, 95% CI = 0.51–0.90). Considering the current evidence, the NCCN guidelines (v. 2.2018) upgraded the solidity of the evidence concerning induction chemotherapy followed by CCRT for locoregionally advanced NPC from level 3 to level 2A, which is the same level as that assigned to CCRT followed by adjuvant chemotherapy.

Clinical trials have established the important role of chemotherapy in locoregionally advanced NPC. The MAC-NPC meta-analysis, which included 19 trials and 4806 patients, confirmed that the addition of chemotherapy to RT significantly improved OS, with an absolute benefit at 5 year reaching 6.3%.[25] Concurrent chemotherapy has been the backbone of treatment, without which induction or adjuvant chemotherapy alone appeared not so effective.[25] Induction chemotherapy and adjuvant chemotherapy could act as supplements to CCRT, with the aim of improving treatment efficiencies.

FUTURE DIRECTIONS IN THE NEXT DECADE

Chemotherapy regimens

For concurrent chemotherapy, cisplatin is the classic drug of choice. Although it is effective, the toxicity profile of cisplatin is moderately harsh, such as gastrointestinal reactions, nephrotoxicity, and ototoxicity. Finding an equivalent drug with lower toxicity will be a research focus. A Phase III clinical trial compared nedaplatin with cisplatin as a concurrent chemotherapy regime in NPC and proposed that nedaplatin was a viable alternative.[26] Another Phase III clinical trial (ChiCTR-TRC-13003285) investigating the feasibility of replacing cisplatin with lobaplatin in induction-concurrent chemotherapy for patients with stage III–IVB NPC (AJCC seventh edition) has completed the recruitment

Table 1. Clinical trials investigating CCRT ± AC in nasopharyngeal carcinoma

Clinical trials	Recruitment period	Phase	Study arms	Chemotherapy regime	No. of patients	Overall survival (5 year)	*p*-value	Progression-free survival (5 year) *p*-value	
Chan 2005	1994–1999	III	CCRT	CC: cisplatin 40 mg/m^2 d1, QW for eight cycles	174	70.3%	0.049	60.2%	0.06
			RT		176	58.6%		52.1%	
Lin 2003	1993–1999	III	CCRT	CC: cisplatin 20 mg/m^2/day d1–4 + fluorouracil 400 mg/m^2/day d1-4, Q4W for two cycles	141	72.3%	0.0022	71.6%	0.0012
			RT		143	54.2%		53.0%	
Wu 2013	2001–2003	III	CCRT	CC: oxaliplatin 70 mg/m^2 d1, QW for eight cycles	59	73.2%	0.028	NR	NR
			RT		56	60.2%		NR	
Chen 2011	2003–2007	III	CCRT	CC: cisplatin 30 mg/m^2 d1, QW for seven cycles	116	94.5%	0.007	87.9%	0.017
			RT		114	85.8%		77.8%	
Al-Sarraf 1998	1989–1995	III	CCRT + AC	CC: cisplatin 100 mg/m^2 d1, Q3W for three cycles AC: cisplatin 80 mg/m^2 d1 + fluorouracil 1000 mg/m^2/day d1-4, Q4W for three cycles	78	67%	0.001	58%	<0.001
			RT		69	37%		29%	
Wee 2005	1997–2003	III	CCRT + AC	CC: cisplatin 25 mg/m^2/day d1-4, Q3W for three cycles AC: cisplatin 20 mg/m^2/day d1–4 + fluorouracil 1000 mg/m^2/day d1-4, Q4W for three cycles	111	67%	0·0077	**59%**	0.032
			RT		110	49%		**46%**	
Lee 2010	1999–2004	III	CCRT + AC	CC: cisplatin 100 mg/m^2 d1, Q3W for three cycles AC: cisplatin 80 mg/m^2 d1 +fluorouracil 1000 mg/m2/day d1-4, Q4W for three cycles	172	68%	0.22	62%	0.035
			RT		176	64%		53%	

CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; CC, concurrent chemotherapy; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks; NR, not reported.

Table 2. Clinical trials investigating IC addition to CCRT in nasopharyngeal carcinoma

Clinical trials	Recruitment period	Phase	Study arms	Chemotherapy regime	No. of patients	Overall survival	*p*-value	Progression-free survival	*P*-value
Hui 2009	2002–2004	II	IC + CCRT	IC: cisplatin 75 mg/m^2 d1 +docetaxel 75 mg/m^2 d1, Q3W for two cycles CC: cisplatin 40 mg/m^2 d1, QW for eight cycles	34	94.1%	0.012	88.2%	0.12
			CCRT		31	67.7%		59.5%	
Fountzilas 2012	2003–2008	II	IC + CCRT	IC: epirubicin 75 mg/m^2 d1 +paclitaxel 175 mg/m^2 d1 +cisplatin 75 mg/m^2 d2, Q3W for three cycles CC: cisplatin 40 mg/m^2 d1, QW for eight cycles	72	70%	0.89	65%	0.38
			CCRT		69	59%		64%	
Tan 2015	2004–2012	II/III	IC + CCRT	IC: carboplatin AUC = 2.5 d1 +gemcitabine 1000 mg/m^2 d1, d8 +paclitaxel 70 mg/m^2 d1, d8, Q3W for three cycles CC: cisplatin 40 mg/m^2 d1, QW for eight cycles	86	94.3%	0.494	74.9%	0.362
			CCRT		86	92.3%		67.4%	
Sun 2016	2011–2013	III	IC +CCRT	IC: cisplatin 60 mg/m^2 d1 +docetaxel 60 mg/m^2 d1 +fluorouracil 600 mg/m^2/day d1-5, Q3W for three cycles CC: cisplatin 100 mg/m^2 d1, Q3W for three cycles	241	92%	0.029	80%	0·034
			CCRT		239	86%		72%	
Cao 2017	2008–2015	III	IC +CCRT	IC: cisplatin 80 mg/m^2 d1 +fluorouracil 800 mg/m^2/day d1-5, Q3W for two cycles CC: cisplatin 80 mg/m^2 d1, Q3W for three cycles	238	88.2%	0.815	82.0%	0.028
			CCRT		238	88.5%		74.1%	
Frikha 2018	2009–2012	III	IC +CCRT	IC: docetaxel 75 mg/m^2 d1 +cisplatin 75 mg/m^2 d1 +fluorouracil 750 mg/m^2/day d1-5, Q3W for three cycles CC: cisplatin 40 mg/m^2 d1, QW for seven cycles	42	86.3%	0.059	73.9%	0.042
			CCRT		41	68.9%		57.2%	
Hong 2018	2003–2009	III	IC +CCRT	IC: mitomycin 8 mg/m^2 d1 +epirubicin 60 mg/m^2 d1 +cisplatin 60 mg/m^2 d1 +fluorouracil 450 mg/m^2 d8 +leucovorin 30 mg/m^2 d8, Q3W CC: cisplatin 30 mg/m^2 d1, QW	239	72%	0.62	61%	0.026
			CCRT		240	68%		50%	

IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CC, concurrent chemotherapy;QW, every week; Q3W, every 3 weeks.
3-year survival results are presented, except that the 5 year results are presented for the trial Hong 2018.

phase, and results of this trial are expected. Similarly, an ongoing clinical trial (NCT03503136) with a 2 × 2 factorial design aims to compare the efficiency and safety of nedaplatin versus cisplatin, and capecitabine *vs* fluorouracil, in induction-concurrent chemotherapy for patients with stage III–IVA NPC (except T3-4N0, AJCC eighth edition).

For induction chemotherapy, different platinum-based regimes have been used in clinical trials; however, no significant differences in survival between different induction chemotherapy regimens were detected in the network meta-analysis.[24] Although the induction regimen of docetaxel plus cisplatin plus fluorouracil (TPF) was proven to be superior to cisplatin plus fluorouracil (PF) for patients with unresectable non-metastatic head and neck squamous cell carcinoma treated with induction chemotherapy followed by CCRT,[27] whether this is the same situation in the setting of locoregionally advanced NPC remains to be determined. An ongoing Phase III clinical trial (NCT02940925) aims to compare two induction chemotherapy regimens directly: PF versus taxol plus cisplatin plus capecitabine (TPC), and the results are eagerly expected. Zhang et al established gemcitabine plus cisplatin (GP), rather than PF, as the standard first-line treatment option for patients with recurrent/metastatic NPC.[28] The convenient medication method of gemcitabine (intravenously on days 1 and 8) and its confirmed efficacy make GP a favorable regimen in locoregionally advanced NPC. A Phase III clinical trial (NCT01872962) aiming to evaluate the therapeutic efficiency of GP as induction chemotherapy in addition to CCRT for patients with Stage III–IVB NPC (except T3-4N0, AJCC seventh edition) has completed the recruitment phase, and results will help us to gain a more comprehensive understanding of the role of induction chemotherapy in locoregionally advanced NPC.

Poor compliance with adjuvant chemotherapy after CCRT may mask its efficiency. Finding tolerable regimens for adjuvant chemotherapy may benefit patients with locoregionally advanced NPC. Metronomic chemotherapy, which refers to the regular administration of low, less-toxic doses of chemotherapeutic drugs for prolonged periods of time, is characterized by its effectiveness and reduced toxicity.[29] Retrospective studies indicated that adjuvant chemotherapy administered in a metronomic manner was effective in high-risk patients with NPC, including those with a positive EBV DNA post RT.[30,31] Clinical trials are needed to confirm the efficiency of metronomic chemotherapy in locoregionally advanced NPC. An ongoing Phase III clinical trial (NCT02958111) is exploring the adjuvant effects of single-agent capecitabine as metronomic chemotherapy in patients with Stage III-IVA NPC (except T3-4N0, T3N1, AJCC eighth edition), and the results are eagerly anticipated. Although adjuvant chemotherapy and induction chemotherapy in addition to CCRT are both level 2A recommendations for locoregionally advance NPC in the NCCN guidelines (v. 2.2018), they have different features and advantages. The question of which one is superior is a concern to clinicians. The NPC-0501 clinical trial recruited six arms and tried to answer this question; the unadjusted comparisons of induction chemotherapy *vs*ersus adjuvant chemotherapy did not reach statistical significance, but adjusted comparisons indicated favorable improvements by induction chemotherapy.[32]

Considering the uncertain results of NPC-0501, a head-to-head comparison between adjuvant chemotherapy and induction chemotherapy is still needed in the future, and we anticipate the results of an ongoing Phase III clinical trial (NCT03306121), which aims to answer this question by comparing TPF followed by CCRT and CCRT followed by PF in high-risk NPC.

De-intensification of treatments

The prolonged survival of patients with locoregionally advanced NPC makes treatment-related toxicities and quality of life important concerns for clinicians when treatment plans are made. Deintensification of treatment in low-risk patients with NPC with good prognosis would be a meaningful direction. There is controversy concerning the need for chemotherapy in Stage II NPC, despite being recommended by the NCCN guidelines. A Phase III clinical trial reported by Chen et al showed that CCRT was associated with a considerable survival benefit for patients with Stage II NPC, at the cost of more acute adverse events, which formed the basis for the recommendation of CCRT for patients with Stage II NPC.[13] However, it should be noted that patients in this trial were treated using two-dimensional RT. In the era of IMRT, RT alone could achieve excellent results in Stage II NPC.[33] Two recent meta-analyses also suggested that CCRT might offer no survival benefit, but might increase toxicities compared with IMRT alone in Stage II NPC.[34,35] Clinical trials are still needed to provide solid evidence to support this notion. An ongoing Phase III non-inferior randomized trial (NCT02633202) aims to determine the value of concurrent chemotherapy for patients with Stage II or T3N0M0 NPC (AJCC seventh edition) treated with IMRT, and results of this trial will have the potential to change the guidelines. It has to be noted that this clinical trial excludes patients with neck lymph node of maximal axial diameter ≥30 mm or pretreatment plasma Epstein–Barr virus (EBV) DNA levels of ≥4000 copies/mL, as these patients are more likely to fail distantly and benefit from CCRT.[36]

As mentioned above, concurrent chemotherapy seems to be more potent than induction chemotherapy and adjuvant chemotherapy.[25] However, the period of CCRT is the hardest time for patients, as some acute toxicities, such as mucositis, vomiting, dysphagia, and weight loss, are very common and severe during this time. A retrospective study showed that induction chemotherapy followed by RT could achieve similar survival outcomes, but fewer acute toxicities, during RT compared with CCRT for patients with T3-4N0-1M0 NPC (AJCC seventh edition).[37] The feasibility of staggering RT and chemotherapy is worth investigation in the future. An ongoing Phase III clinical trial (NCT03366415) aims to compare the efficacy and safety of induction chemotherapy followed by RT and adjuvant chemotherapy with induction chemotherapy followed by CCRT in patients with III–IVA NPC (AJCC eighth edition). Another Phase III clinical trial (NCT02434614) aims to prove the non-inferiority of induction chemotherapy followed by RT compared with induction chemotherapy followed by CCRT for patients with III–IVB NPC (AJCC seventh edition). The results of these trials will help us redefine the necessity of concurrent chemotherapy in locoregionally advanced NPC.

Nodal metastasis in NPC progresses in an orderly manner. The retropharyngeal lymph nodes and level II lymph nodes are most commonly involved, followed by the level III and level V, level IV, and supraclavicular fossa lymph nodes; while nodal skipping metastasis is rare.[38] The patterns of nodal metastasis in NPC make elective prophylactic irradiation to the lymph drainage area possible.[39] An ongoing Phase III clinical trial (NCT02642107) aims to compare elective neck irradiation to whole neck irradiation in T1-4N0-1M0 NPC (AJCC seventh edition). Another ongoing Phase III clinical trial (NCT03346109) aims to test the feasibility of sparing medial group retropharyngeal node irradiation in T1-4N0-3M0 NPC (except for medial group retropharyngeal node metastasis, AJCC eighth edition). Both trials are a non-inferior design, expecting similar disease control between the arms and fewer RT-related toxicities for the elective irradiation arm, such as hypothyroidism and dysphagia. Yang et al[40] conducted a clinical trial and reported that reducing the IMRT target volume after induction chemotherapy did not reduce the local control and survival rate in locoregionally advanced NPC but the life quality of patients were improved. In the future, more evidences about the feasibility de-intensification of RT are needed.

Personalized therapy

In the era of precision medicine, the heterogeneity of patients with NPC makes personalized therapy necessary. However, there is still a long way to go in applying personalized therapy in clinical practice. The NCCN guidelines (v. 2.2018) still recommend the same treatments, namely CCRT with or without adjuvant chemotherapy or induction chemotherapy, for locoregionally advanced NPC, namely the Stage II–IVA NPC (AJCC eighth edition). However, these recommendations are only merely based on the TNM staging system, which is anatomy-based. Therefore, much work remains to be done to refine these guidelines and make them more precise through clinical trials in the next decade.

Retrospective studies revealed that plasma EBV DNA, tumor volume, and serum lactate dehydrogenase might be important supplements to anatomical TNM staging in tailoring treatments for patients with NPC.[41–43] Among them, plasma EBV DNA is the most important biomarker. Plasma EBV DNA is regarded as a circulating tumor DNA from NPC, reflecting not only the tumor burden, but also other tumor features, such as accessibility to circulation, tumor cell kinetics, metabolic activity, and metastatic potential.[44] Its utility in screening, prognosis, staging, and surveillance has been investigated.[45–48] The value of plasma EBV DNA in guiding treatment of NPC has becomes a hot research topic.[49] The first reported clinical trial using EBV DNA in stratified therapy for patients with NPC was the Hong Kong NPC Study Group 0502 trial.[50] In this trial, 104 patients with detectable plasma EBV DNA after RT were randomly assigned to a GP adjuvant chemotherapy arm or a clinical observation arm. Based on intent-to-treat analysis, no improvement in prognosis was associated with adjuvant chemotherapy, which might have been caused by the resistance of residual subclinical disease to cisplatin-based adjuvant chemotherapy after cisplatin-based concurrent chemotherapy in that study. Another noteworthy clinical trial is NRG-HN001 (NCT02135042), which was initiated by the NRG Oncology Cooperative Group. This trial used post-RT plasma EBV DNA measurements to divide patients with NPC into low-risk and high-risk groups, with the hypothesis that the low-risk group would not need adjuvant chemotherapy and the high-risk group would benefit from more-aggressive, non-cross-resistant paclitaxel and gemcitabine chemotherapy. Another clinical trial (NCT02363400) also tried to utilize post-RT plasma EBV DNA levels to guide adjuvant chemotherapy for NPC. In addition, pretreatment EBV DNA levels may also be valuable in tailoring treatment. An ongoing Phase II clinical trial (NCT02871518) was designed to assess the efficacy of two cycles of concurrent chemotherapy compared with three cycles of concurrent chemotherapy for low-risk patients with Stage III–IVB NPC (AJCC seventh edition), identified using pretreatment EBV DNA levels of <4000 copies/mL.

Unfavorable EBV DNA response after induction chemotherapy or at the midpoint of RT is also proved to be an adverse prognosticator for clinical outcome.[51,52] These observations raised the possibility of incorporating EBV DNA levels for risk-stratified treatment adaptation, based on liquid biopsy of biomarker responses. Studies with dense longitudinal EBV DNA surveillance data are warranted to further illustrate the association of the EBV DNA response during treatment to prognoses, and the utility of real-time information on the treatment response for therapeutic adaptation. A Phase II clinical trial (NCT03668730) aims to investigate the feasibility of reducing the radiation dose to 60 Gy for low risk patients with Stage III NPC (AJCC eighth edition), identified using pretreatment EBV DNA levels of <4000 copies/mL, radiographical complete response/partial response, and undetectable plasma EBV DNA after two cycles of TPF induction chemotherapy. We believe the results of these trials will help us improve personalized therapy and move forward toward precision medicine.

Novel therapies

Even with the best available treatment in modern practice, around 5–15% of patients develop local failure, and 15–30% develop distant failure.[53] It seems that conventional chemotherapy has reached a therapeutic ceiling in locoregionally advanced NPC. In the next decade, applying novel therapies to clinical practice to further improve the outcome of patients with locoregionally advanced NPC will be a research trend. Targeted therapy and immunotherapy are representative novel therapies.

Targeted therapies against epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) and its receptor (VEGFR) have been explored; however, most studies were either retrospective or Phase II conducted in recurrent/metastatic NPC, which could only provide low-quality evidence. Anti EGFR monoclonal antibodies, such as cetuximab and nimotuzumab, are the most frequently investigated among these targeted therapies, and are often used clinically to treat locoregionally advanced NPC in China, which is recommended by the China guidelines for NPC. A meta-analysis based on retrospective studies and Phase II clinical trials found that anti EGFR monoclonal antibodies additional to conventional chemotherapy

might enhance treatment efficiency in locoregionally advanced NPC.[54] In the future, Phase III clinical trials are warranted to provide more consolidated evidence.

The widespread existence of Type II latent EBV infection and immunosuppression status in non-keratinizing NPC make immunotherapy a promising strategy. Immunotherapy targeted against EBV antigens has been previously explored in clinical trials. A Phase II clinical trial assessed the role of chemotherapy followed by autologous EBV-specific cytotoxic T lymphocytes transfusion in 38 patients with recurrent/metastatic NPC, and achieved an encouraging response rate of 71.4%, with 3 complete and 22 partial responses.[55] A Phase III clinical trial (NCT02578641) using this protocol is currently under way. Li et al reported that autologous cytokine-induced killer cell transfusion combined with chemotherapy was an effective treatment for patients with metastatic NPC.[56] A therapeutic cancer vaccine[57] is also being tested in patients with incurable NPC after conventional therapy in a Phase II clinical trial (NCT01094405). In the future, immunotherapy strategies should be evaluated in locoregionally advanced NPC to enhance treatment, but only after their efficacy and safety have been demonstrated in refractory NPC.

Another immunotherapy strategy is the use of immune checkpoint inhibitors (ICIs). As its name suggests, the immune checkpoint pathways can hold immune response in check, which normally maintain self-tolerance and limit collateral tissue damage during anti-microbial immune responses.[58] Malignant tumours can co-opt these inhibitory pathways and evade immune destruction, which provide the rationality for the use of ICIs, such as anti-cytotoxic T lymphocyte antigen 4 (anti-CTLA-4), anti-Programmed Death 1 (anti-PD-1), and anti-Programmed Death Ligand 1 (anti-PD-L1), to unleash anti-tumor immunity and mediate durable tumor regression.[58] Last decade has witnessed ICIs' success in the treatment of many malignancies, including melanoma and non-small cell lung cancer (NSCLC).[59,60] Several Phase III clinical trials have confirmed ICIs' superiority over docetaxel in patients with platinum-refractory advanced NSCLC in terms of OS.[61–64] On the basis of these trials, the US Food and Drug Administration has approved nivolumab, atezolizumab, and pembrolizumab as second-line therapy for advanced NSCLC. The KEYNOTE-024 trial compared pembrolizumab with platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC with PD-L1 tumor proportion score (TPS) of 50% or greater, and found that pembrolizumab monotherapy could improve OS and PFS significantly.[65] Further, KEYNOTE-042 trial reported pembrolizumab's efficiency in patients with PD-L1 TPS of 1% or greater in the first-line setting.[66] However, the CheckMate-026 trial which compared first-line nivolumab with platinum-based chemotherapy in patients with recurrent/metastatic NSCLC with PD-L1 TPS of 5% or greater reported that nivolumab failed to improve PFS or OS.[67] The lack of survival benefit in CheckMate-026 may be due to the patient selection primarily,[68] which also reflect the complex biology of immune checkpoint pathways. Besides ICIs monotherapy, combination strategies are also being profoundly investigated. The combination of pembrolizumab and chemotherapy was proved to be superior to chemotherapy alone in metastatic NSCLC in the first-line setting by two Phase III clinical trails.[69,70] CheckMate-227 trial reported that PFS among recurrent/metastatic NSCLC patients with a high tumor mutational burden was significantly longer with nivolumab plus ipilimumab than with chemotherapy.[71] Another Phase III clinical trial reported that durvalumab following chemoradiotherapy could significantly improve PFS in patients with locally advanced, unresectable NSCLC compared with placebo following chemoradiotherapy.[72]

ICIs' success in NSCLC may be repeated in NPC. Several early phase clinical trials showed that ICIs could have a promising effect on recurrent/metastatic NPC. Hsu et al reported in a Phase Ib multicohort trial that pembrolizumab could achieve an objective response rate of 25.9% in patients with recurrent/metastatic NPC.[73] Ma et al also reported a similar response rate of 20.5% to nivolumab in patients with recurrent/metastatic NPC in a Phase II trial.[74] Fang et al reported the results of two Phase I trials: (NCT02721589), in which camrelizumab monotherapy could achieve an overall response rate of 34% for patients with recurrent/metastatic NPC who received at least one previous line of treatment; and (NCT03121716), in which camrelizumab combined with GP could achieve an overall response rate of 91% in treatment-naive patients with recurrent/metastatic NPC.[75] In the setting of locoregionally advanced NPC, several clinical trials exploring the efficacy of immune checkpoint inhibitors of are under way. A single-arm Phase II trial (NCT03544099) is attempting to explore the efficacy of pembrolizumab in patients with NPC with detectable plasma EBV DNA after curative chemoradiation. Another Phase III clinical trial (NCT03427827) is exploring the efficacy of camrelizumab as an adjuvant therapy following induction chemotherapy plus CCRT in patients with Stage III–IVA NPC (except T3N1M0 and T3-4N0M0, AJCC eighth edition). The efficacy of pembrolizumab when incorporated into the induction, concurrent, and adjuvant phase of treatment in patients with stage IVA NPC (AJCC eighth edition) is also being investigated in a single-arm Phase II clinical trial (NCT03734809). In the near future, clinical trials investigating different strategies of combining chemoradiotherapy and ICIs and identifying NPC patients who would most likely benefit from immunotherapy will be a worthy research direction.

CONCLUSION

Clinical trials are effective weapons in the war against NPC. Current treatment modalities for NPC are based on evidence provided by previous clinical trials. Future clinical trials will provide the basis of changing and improving current treatment guidelines for NPC. However, with limited resources for clinical trials, clinical trialists should be highly selective about which questions should be answer. The correct directions for the clinical trials will help to avoid wasting resources and will benefit patients. We proposed four directions for clinical trials in locoregionally advanced NPC: (1) Continue refining current regimens of chemotherapy; (2) de-intensify treatment for specific groups of patients; (3) develop personalized treatment based on predictors, such as plasma EBV DNA; and (4) investigate novel therapies, such as targeted therapy and immunotherapy. We believe

that clinical trials have a promising future for the treatment of locoregionally advanced NPC.

FUNDING

This work was supported by the Natural Science Foundation of Guang Dong Province [grant number 2017A030312003], the Health & Medical Collaborative Innovation Project of Guangzhou City, China [grant number 201803040003], the Innovation Team Development Plan of the Ministry of Education [grant number IRT_17R110], and the Overseas Expertise Introduction Project for Discipline Innovation (111 Project) [grant number B14035].

REFERENCES

1. Wei K-R, Zheng R-S, Zhang S-W, Liang Z-H, Li Z-M, Chen W-Q. Nasopharyngeal carcinoma incidence and mortality in China, 2013. *Chin J Cancer* 2017; **36**: 90. doi: https://doi.org/10.1186/s40880-017-0257-9
2. ChuaMLK, WeeJTS, HuiEP, ChanATC. Nasopharyngeal carcinoma. *The Lancet* 2016; **387**: 1012–24. doi: https://doi.org/10.1016/S0140-6736(15)00055-0
3. Au KH, Ngan RKC, Ng AWY, Poon DMC, Ng WT, Yuen KT, et al. Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in Hong Kong: a report of 3328 patients (HKNPCSG 1301 study. *Oral Oncol* 2018; **77**: 16–21. doi: https://doi.org/10.1016/j.oraloncology.2017.12.004
4. LeeAWM, SzeWM, AuJSK, LeungSF, LeungTW, ChuaDTT, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *International Journal of Radiation Oncology Biology Physics* 2005; **61**: 1107–16. doi: https://doi.org/10.1016/j.ijrobp.2004.07.702
5. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. *JCO* 1998; **16**: 1310–7. doi: https://doi.org/10.1200/JCO.1998.16.4.1310
6. Chen Y, Sun Y, Liang S-B, Zong J-F, Li W-F, Chen M, et al. Progress report of a randomized trial comparing long-term survival and late toxicity of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in patients with stage III to IVb nasopharyngeal carcinoma from endemic regions of China. *Cancer* 2013; **119**: 2230–8. doi: https://doi.org/10.1002/cncr.28049
7. Lee AWM, Tung SY, Chua DTT, Ngan RKC, Chappell R, Tung R, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2010; **102**: 1188–98. doi: https://doi.org/10.1093/jnci/djq258
8. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union Against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 2005; **23**: 6730–8. doi: https://doi.org/10.1200/JCO.2005.16.790
9. KwongDLW, ShamJST, AuGKH, ChuaDTT, KwongPWK, ChengACK, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *JCO* 2004; **22**: 2643–53. doi: https://doi.org/10.1200/JCO.2004.05.173
10. Chan ATC, Leung SF, Ngan RKC, Teo PML, Lau WH, Kwan WH, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2005; **97**: 536–9. doi: https://doi.org/10.1093/jnci/dji084
11. LinJ-C, JanJ-S, HsuC-Y, LiangW-M, JiangR-S, WangW-Y. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: Positive effect on overall and progression-free survival. *JCO* 2003; **21**: 631–7. doi: https://doi.org/10.1200/JCO.2003.06.158
12. Wu X, Huang PY, Peng PJ, Lu LX, Han F, Wu SX, et al. Long-term follow-up of a phase III study comparing radiotherapy with or without weekly oxaliplatin for locoregionally advanced nasopharyngeal carcinoma. *Ann Oncol* 2013; **24**: 2131–6. doi: https://doi.org/10.1093/annonc/mdt163
13. Chen Q-Y, Wen Y-F, Guo L, Liu H, Huang P-Y, Mo H-Y, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. *J Natl Cancer Inst* 2011; **103**: 1761–70. doi: https://doi.org/10.1093/jnci/djr432
14. Chen L, Hu C-S, Chen X-Z, Hu G-Q, Cheng Z-B, Sun Y, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2012; **13**: 163–71. doi: https://doi.org/10.1016/S1470-2045(11)70320-5
15. Chen L, Hu C-S, Chen X-Z, Hu G-Q, Cheng Z-B, Sun Y, et al. Adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase 3 multicentre randomised controlled trial. *Eur J Cancer* 2017; **75**: 150–8. doi: https://doi.org/10.1016/j.ejca.2017.01.002
16. Chen YP, Wang ZX, Chen L, Liu X, Tang LL, Mao YP, et al. A Bayesian network meta-analysis comparing concurrent chemoradiotherapy followed by adjuvant chemotherapy, concurrent chemoradiotherapy alone and radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *Ann Oncol* 2015; **26**: 205–11. doi: https://doi.org/10.1093/annonc/mdu507
17. Ribassin-Majed L, Marguet S, Lee AWM, Ng WT, Ma J, Chan ATC, et al. What is the best treatment of locally advanced nasopharyngeal carcinoma? an individual patient data network meta-analysis. *JCO* 2017; **35**: 498–505. doi: https://doi.org/10.1200/JCO.2016.67.4119
18. Hui EP, Ma BB, Leung SF, King AD, Mo F, Kam MK, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol* 2009; **27**: 242–9. doi: https://doi.org/10.1200/JCO.2008.18.1545
19. TanT, LimW-T, FongK-W, CheahS-L, SoongY-L, AngM-K, et al. Concurrent chemo-radiation with or without induction gemcitabine, carboplatin, and paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. *International Journal of Radiation*

Oncology Biology Physics 2015; **91**: 952–60. doi: https://doi.org/10.1016/j.ijrobp.2015.01.002

20. Sun Y, Li W-F, Chen N-Y, Zhang N, Hu G-Q, Xie F-Y, 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: https://doi.org/10.1016/S1470-2045(16)30410-7
21. Cao S-M, Yang Q, Guo L, Mai H-Q, Mo H-Y, Cao K-J, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase III multicentre randomised controlled trial. *Eur J Cancer* 2017; **75**: 14–23. doi: https://doi.org/10.1016/j.ejca.2016.12.039
22. Frikha M, Auperin A, Tao Y, Elloumi F, Toumi N, Blanchard P, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02. *Ann Oncol* 2018; **29**: 731–6. doi: https://doi.org/10.1093/annonc/mdx770
23. Hong RL, Hsiao CF, Ting LL, Ko JY, Wang CW, Chang JTC, et al. Final results of a randomized phase III trial of induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in patients with stage IVA and IVb nasopharyngeal carcinoma-Taiwan Cooperative Oncology Group (TCOG) 1303 study. *Ann Oncol* 2018; **29**: 1972–9. doi: https://doi.org/10.1093/annonc/mdy249
24. Chen Y-P, Tang L-L, Yang Q, Poh S-S, Hui EP, Chan ATC, et al. Induction chemotherapy plus concurrent chemoradiotherapy in endemic nasopharyngeal carcinoma: individual patient data pooled analysis of four randomized trials. *Clin Cancer Res* 2018; **24**: 1824–33. doi: https://doi.org/10.1158/1078-0432.CCR-17-2656
25. Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol* 2015; **16**: 645–55. doi: https://doi.org/10.1016/S1470-2045(15)70126-9
26. Tang L-Q, Chen D-P, Guo L, Mo H-Y, Huang Y, Guo S-S, et al. Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised phase 3 trial. *Lancet Oncol* 2018; **19**: 461–73. doi: https://doi.org/10.1016/S1470-2045(18)30104-9
27. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 2007; **357**: 1705–15. doi: https://doi.org/10.1056/NEJMoa070956
28. Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *The Lancet* 2016; **388**: 1883–92. doi: https://doi.org/10.1016/S0140-6736(16)31388-5
29. Bocci G, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: a neglected but crucial aspect. *Nat Rev Clin Oncol* 2016; **13**: 659–73. doi: https://doi.org/10.1038/nrclinonc.2016.64
30. TwuC-W, WangW-Y, ChenC-C, LiangK-L, JiangR-S, WuC-T, et al. Metronomic adjuvant chemotherapy improves treatment outcome in nasopharyngeal carcinoma patients with postradiation persistently detectable plasma Epstein-Barr virus deoxyribonucleic acid. *International Journal of Radiation Oncology*Biology*Physics* 2014; **89**: 21–9. doi: https://doi.org/10.1016/j.ijrobp.2014.01.052
31. Liu Y-C, Wang W-Y, Twu C-W, Jiang R-S, Liang K-L, Wu C-T, et al. Prognostic impact of adjuvant chemotherapy in high-risk nasopharyngeal carcinoma patients. *Oral Oncol* 2017; **64**: 15–21. doi: https://doi.org/10.1016/j.oraloncology.2016.11.008
32. Lee AWM, Ngan RKC, Tung SY, Cheng A, Kwong DLW, Lu T-X, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer* 2015; **121**: 1328–38. doi: https://doi.org/10.1002/cncr.29208
33. Su S-F, Han F, Zhao C, Chen C-Y, Xiao W-W, Li J-X, SFS, JXL, et al. Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone. *Int J Radiat Oncol Biol Phys* 2012; **82**: 327–33. doi: https://doi.org/10.1016/j.ijrobp.2010.09.011
34. Xu C, Zhang L-H, Chen Y-P, Liu X, Zhou G-Q, Lin A-H, et al. Chemoradiotherapy versus radiotherapy alone in stage II nasopharyngeal carcinoma: a systemic review and meta-analysis of 2138 patients. *J Cancer* 2017; **8**: 287–97. doi: https://doi.org/10.7150/jca.17317
35. Liu F, Jin T, Liu L, Xiang Z, Yan R, Yang H. The role of concurrent chemotherapy for stage II nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: a systematic review and meta-analysis. *PLoS One* 2018; **13**: e0194733. doi: https://doi.org/10.1371/journal.pone.0194733
36. Du X-J, Tang L-L, Mao Y-P, Guo R, Sun Y, Lin A-H, et al. Circulating EBV DNA, globulin and nodal size predict distant metastasis after intensity-modulated radiotherapy in stage II nasopharyngeal carcinoma. *J Cancer* 2016; **7**: 664–70. doi: https://doi.org/10.7150/jca.14183
37. Yao J-J, Yu X-L, Zhang F, Zhang W-J, Zhou G-Q, Tang L-L, et al. Radiotherapy with neoadjuvant chemotherapy versus concurrent chemoradiotherapy for ascending-type nasopharyngeal carcinoma: a retrospective comparison of toxicity and prognosis. *Chin J Cancer* 2017; **36**: 26. doi: https://doi.org/10.1186/s40880-017-0195-6
38. Tang L, Mao Y, Liu L, Liang S, Chen Y, Sun Y, et al. The volume to be irradiated during selective neck irradiation in nasopharyngeal carcinoma: analysis of the spread patterns in lymph nodes by magnetic resonance imaging. *Cancer* 2009; **115**: 680–8. doi: https://doi.org/10.1002/cncr.24049
39. Huang C-L, Xu C, Zhang Y, Zhou G-Q, Mao Y-P, Liu Q, et al. Feasibility of ipsilateral lower neck sparing irradiation for unilateral or bilateral neck node-negative nasopharyngeal carcinoma: systemic review and meta-analysis of 2, 521 patients. *Radiat Oncol* 2018; **13**: 141. doi: https://doi.org/10.1186/s13014-018-1087-x
40. Yang H, Chen X, Lin S, Rong J, Yang M, Wen Q, et al. Treatment outcomes after reduction of the target volume of intensity-modulated radiotherapy following induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: a prospective, multi-center, randomized clinical trial. *Radiother Oncol* 2018; **126**: 37–42. doi: https://doi.org/10.1016/j.radonc.2017.07.020
41. Guo R, Sun Y, Yu X-L, Yin W-J, Li W-F, Chen Y-Y, et al. Is primary tumor volume still a prognostic factor in intensity modulated radiation therapy for nasopharyngeal carcinoma? *Radiother Oncol* 2012; **104**: 294–9. doi: https://doi.org/10.1016/j.radonc.2012.09.001
42. Zhou G-Q, Ren X-Y, Mao Y-P, Chen L, Sun Y, Liu L-Z, et al. Prognostic implications of dynamic serum lactate dehydrogenase assessments in nasopharyngeal carcinoma

patients treated with intensity-modulated radiotherapy. *Sci Rep* 2016; **6**: 22326. doi: https://doi.org/10.1038/srep22326
43. Peng L, Chen Y-P, Xu C, Tang L-L, Chen L, Lin A-H, et al. A novel scoring model to predict benefit of additional induction chemotherapy to concurrent chemoradiotherapy in stage II-IVa nasopharyngeal carcinoma. *Oral Oncol* 2018; **86**: 258–65. doi: https://doi.org/10.1016/j.oraloncology.2018.10.007
44. PengL, YangY, GuoR, MaoYP, XuC, ChenYP, et al. Relationship between pretreatment concentration of plasma Epstein-Barr virus DNA and tumor burden in nasopharyngeal carcinoma: an updated interpretation. *Cancer Med* 2018;.
45. ChanKCA, WooJKS, KingA, ZeeBCY, LamWKJ, ChanSL, et al. Analysis of plasma Epstein–Barr virus DNA to screen for nasopharyngeal cancer. *N Engl J Med* 2017; **377**: 513–22. doi: https://doi.org/10.1056/NEJMoa1701717
46. Leung S-fai, Zee B, Ma BB, Hui EP, Mo F, Lai M, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. *JCO* 2006; **24**: 5414–8. doi: https://doi.org/10.1200/JCO.2006.07.7982
47. Guo R, Tang L-L, Mao Y-P, Du X-J, Chen L, Zhang Z-C, et al. Proposed modifications and incorporation of plasma Epstein-Barr virus DNA improve the TNM staging system for Epstein-Barr virus-related nasopharyngeal carcinoma. *Cancer* 2019; **125**: 79–89. doi: https://doi.org/10.1002/cncr.31741
48. Li W-F, Zhang Y, Huang X-B, Du X-J, Tang L-L, Chen L, et al. Prognostic value of plasma Epstein-Barr virus DNA level during posttreatment follow-up in the patients with nasopharyngeal carcinoma having undergone intensity-modulated radiotherapy. *Chin J Cancer* 2017; **36**: 87. doi: https://doi.org/10.1186/s40880-017-0256-x
49. Kim KY, Le Q-T, Yom SS, Ng RHW, Chan KCA, Bratman SV, et al. Clinical utility of Epstein-Barr virus DNA testing in the treatment of nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys* 2017; **98**: 996–1001. doi: https://doi.org/10.1016/j.ijrobp.2017.03.018
50. Chan ATC, Hui EP, Ngan RKC, Tung SY, Cheng ACK, Ng WT, , et al. Analysis of plasma Epstein-Barr virus DNA in nasopharyngeal cancer after chemoradiation to identify high-risk patients for adjuvant chemotherapy: a randomized controlled trial. *J Clin Oncol* 2018;: Jco2018777847. doi: https://doi.org/10.1200/JCO.2018.77.7847
51. Liu L-T, Tang L-Q, Chen Q-Y, Zhang L, Guo S-S, Guo L, et al. The prognostic value of plasma Epstein-Barr viral DNA and tumor response to neoadjuvant chemotherapy in advanced-stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2015; **93**: 862–9. doi: https://doi.org/10.1016/j.ijrobp.2015.08.003
52. Leung SF, Chan KCA, Ma BB, Hui EP, Mo F, Chow KCK, et al. Plasma Epstein-Barr viral DNA load at midpoint of radiotherapy course predicts outcome in advanced-stage nasopharyngeal carcinoma. *Ann Oncol* 2014; **25**: 1204–8. doi: https://doi.org/10.1093/annonc/mdu117
53. Lee AWM, Ma BBY, Ng WT, Chan ATC, . Management of nasopharyngeal carcinoma: current practice and future perspective. *J Clin Oncol* 2015; **33**: 3356–64. doi: https://doi.org/10.1200/JCO.2015.60.9347
54. Peng L, Liu Z-L, Xu C, Tang L-L, Liu X, Lin A-H, et al. The efficacy and safety of anti-epidermal growth factor receptor monoclonal antibodies in nasopharyngeal carcinoma: Literature-based meta-analyses. *J Cancer* 2018; **9**: 4510–20. doi: https://doi.org/10.7150/jca.27611
55. Chia W-K, Teo M, Wang W-W, Lee B, Ang S-F, Tai W-M, et al. Adoptive T-cell transfer and chemotherapy in the first-line treatment of metastatic and/or locally recurrent nasopharyngeal carcinoma. *Mol Ther* 2014; **22**: 132–9. doi: https://doi.org/10.1038/mt.2013.242
56. Li J-jun, Gu M-fa, Pan K, Liu L-zhi, Zhang H, Shen W-xi, et al. Autologous cytokine-induced killer cell transfusion in combination with gemcitabine plus cisplatin regimen chemotherapy for metastatic nasopharyngeal carcinoma. *J Immunother* 2012; **35**: 189–95. doi: https://doi.org/10.1097/CJI.0b013e318241d9de
57. Hui EP, Taylor GS, Jia H, Ma BBY, Chan SL, Ho R, et al. Phase I trial of recombinant modified vaccinia Ankara encoding Epstein-Barr viral tumor antigens in nasopharyngeal carcinoma patients. *Cancer Res* 2013; **73**: 1676–88. doi: https://doi.org/10.1158/0008-5472.CAN-12-2448
58. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell* 2015; **27**: 450–61. doi: https://doi.org/10.1016/j.ccell.2015.03.001
59. Franklin C, Livingstone E, Roesch A, Schilling B, Schadendorf D. Immunotherapy in melanoma: recent advances and future directions. *Eur J Surg Oncol* 2017; **43**: 604–11. doi: https://doi.org/10.1016/j.ejso.2016.07.145
60. Rolfo C, Caglevic C, Santarpia M, Araujo A, Giovannetti E, Gallardo CD, et al. Immunotherapy in NSCLC: a promising and revolutionary weapon. *Adv Exp Med Biol* 2017; **995**: 97–125. doi: https://doi.org/10.1007/978-3-319-53156-4_5
61. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 123–35. doi: https://doi.org/10.1056/NEJMoa1504627
62. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced Nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 1627–39. doi: https://doi.org/10.1056/NEJMoa1507643
63. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *The Lancet* 2016; **387**: 1540–50. doi: https://doi.org/10.1016/S0140-6736(15)01281-7
64. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (oak): a phase 3, open-label, multicentre randomised controlled trial. *The Lancet* 2017; **389**: 255–65. doi: https://doi.org/10.1016/S0140-6736(16)32517-X
65. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; **375**: 1823–33. doi: https://doi.org/10.1056/NEJMoa1606774
66. Mok TSK, Wu Y-L, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019; **393**: 1819–30. doi: https://doi.org/10.1016/S0140-6736(18)32409-7
67. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med* 2017; **376**: 2415–26. doi: https://doi.org/10.1056/NEJMoa1613493
68. Remon J, Besse B, Soria J-C. Successes and failures: what did we learn from recent first-line treatment immunotherapy trials in non-small cell lung cancer? *BMC Med* 2017;

15: 55. doi: https://doi.org/10.1186/s12916-017-0819-3

69. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018; **379**: 2040–51. doi: https://doi.org/10.1056/NEJMoa1810865
70. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378**: 2078–92. doi: https://doi.org/10.1056/NEJMoa1801005
71. Hellmann MD, Ciuleanu T-E, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; **378**: 2093–104. doi: https://doi.org/10.1056/NEJMoa1801946
72. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; **377**: 1919–29. doi: https://doi.org/10.1056/NEJMoa1709937
73. Hsu C, Lee S-H, Ejadi S, Even C, Cohen RB, Le Tourneau C, 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: https://doi.org/10.1200/JCO.2017.73.3675
74. Ma BBY, Lim W-T, Goh B-C, Hui EP, Lo K-W, Pettinger A, et al. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the Mayo Clinic phase 2 Consortium (NCI-9742. *J Clin Oncol* 2018; **36**: 1412–8. doi: https://doi.org/10.1200/JCO.2017.77.0388
75. Fang W, Yang Y, Ma Y, Hong S, Lin L, He X, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. *Lancet Oncol* 2018; **19**: 1338–50. doi: https://doi.org/10.1016/S1470-2045(18)30495-9