

Commentary

Current Treatment Landscape of Nasopharyngeal Carcinoma and Potential Trials Evaluating the Value of Immunotherapy

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Abstract

Nasopharyngeal carcinoma (NPC) is a type of head and neck cancer with a distinctive regional and racial prevalence. It is associated with Epstein Barr Virus infection and has a high propensity for regional and distant metastases, while at the same time it is very sensitive to radiation and chemotherapy. A common feature of Epstein Barr Virus-positive NPC is the dense infiltration of lymphocytes in the tumor stroma and positive PD-L1 expression in tumor cells, making it an attractive target for immunotherapy, especially immune checkpoint inhibitors. As new immunotherapeutic agents are being rapidly adopted in many cancers, including head and neck cancer, the National Cancer Institute sponsored a Clinical Trial Planning Meeting to identify opportunities for developing phase II and III trials testing immunotherapy in different stages of NPC. The meeting started with the summary of the biology of the disease, current standards of care and evidence of immunotherapy in this cancer. Three subcommittees were tasked to develop clinical trials: loco-regionally advanced, non-metastatic NPC; widely metastatic NPC; and either local-recurrence after initial treatment or presenting with oligometastatic disease. This article summarizes the proceedings of this Clinical Trial Planning Meeting and provides a roadmap for future trials incorporating immune checkpoint inhibitors for therapeutic management of NPC. This roadmap, though specific for NPC, may also be applicable to other virally-driven cancers that have similar ability to evade the host's immune system.

GLOBOCAN-2018 estimates that there will be 129,079 new cases of nasopharyngeal carcinoma (NPC) worldwide in 2018 and 72,987 will die of this cancer.¹ NPC is intimately linked to infection by the Epstein Barr Virus (EBV)^{2,3} and exhibits marked racial and geographical predilection. Most cases occur in Asia and North Africa. In the United States, it is rare among Caucasians but is common among ethnic Asians. With its peak age incidence between 40 to 60 years,⁴ its socioeconomic impact is considerable.

Recent advances in immune check point inhibitors (ICI) in head and neck cancer, specifically in virally-driven neoplasms such as the human papillomavirus (HPV)-associated oropharyngeal carcinoma and Merkel cell cancer, have stimulated interest in testing ICI in NPC. Moreover, three phase I-II trials have demonstrated promising response rates to the anti-programmed cell death-1 (PD1) targeted therapy in heavily pretreated NPC patients with recurrent/metastatic disease.⁵⁻⁷ This led to the National Cancer Institute (NCI)'s approval to convene a clinical trial planning meeting (CTPM) focusing on immunotherapy in NPC.

The meeting, which was held on February 27-28, 2018, in Phoenix, Arizona, gathered 40 NPC and immunotherapy experts from different disciplines (medical oncologists, radiation oncologists, surgical oncologists, immunologists, translational researchers, statisticians and industry partners) from primarily North America and Asia. The group reviewed the current management of NPC and the available data on immunotherapy and biomarkers in order to design the best possible clinical trials for improving outcomes. The meeting comprehensively covered clinical scenarios including locoregional, recurrent and metastatic (oligo-metastatic and widely metastatic) disease states. This paper provides an overview of the current landscape, a summary of the issues for improvement, and the proposed immunotherapy trials in NPC. Since all

proposed trials focus on ICI, specifically anti PD1/PD-L1 antibodies, similar biomarkers are proposed for all trials and are summarized in the biomarker section.

Locoregionally-Advanced Nasopharyngeal Carcinoma

Chemoradiation regimens

Owing to advances in imaging and radiation (RT) techniques, substantial improvement in loco-regional control and toxicity reduction have been observed in the standard treatment of locoregionally-advanced NPC. Intensity-modulated radiotherapy (IMRT) is the primary treatment for patients with non-disseminated NPC. For patients with locoregionally-advanced NPC, the addition of concomitant (cisplatin-based) chemotherapy with or without sequential chemotherapy is recommended as evidenced by multiple randomized trials and meta-analyses. The long-term update of NPC-9901 and NPC-9902 Trials⁸ confirmed that concurrent chemoradiation (CRT) yielded statistically significant improvement in 10-year progression free (PFS) and overall survival (OS) over RT alone. There was no statistically significant increase in late toxicity or non-cancer deaths. Exploratory analyses showed that only patients who could tolerate ≥ 2 chemotherapy cycles in both the concurrent and adjuvant phases achieved statistically significant improvement in distant control (73% vs. 65%, $p = 0.037$) and maximum survival gain.⁹ The ability to deliver adjuvant chemotherapy is poor in NPC patients because they are still recuperating from the acute CRT toxicities. Therefore, distant failure (~20-30%) remains the leading cause of death in NPC.

Instead of adding adjuvant chemotherapy to CRT in all stage III-IVA patients, it would be ideal if this were restricted to those with high risk of failure following CRT. Outside of the T- and N-staging, circulating EBV-DNA is the most promising biomarker to date. Studies have

shown that a detectable circulating EBV-DNA after CRT is associated with poor prognosis for EBV⁺ NPC, and conversely, patients with undetectable circulating EBV-DNA have an excellent prognosis.^{2,10-14} EBV-DNA testing by real-time PCR is extremely sensitive to the conditions of detection; therefore, harmonization of different CLIA (Clinical Laboratory Improvement Amendment) certified or equivalent laboratories is needed to provide reproducible results worldwide.¹⁵ Le et al. have demonstrated that after harmonization, the reproducibility and interclass correlation between the different laboratories can be very high.¹⁶ The combined phase II-III NRG-Oncology HN001 trial (NCT02135042) is testing the feasibility of using plasma EBV-DNA following CRT to personalize adjuvant treatment.

Recent reports from randomized phase III trials comparing induction chemotherapy followed by CRT (C-CRT) versus CRT alone have shown statistically significant PFS benefit with C-CRT. The trial by Sun et al.¹⁷ using modified Docetaxel-Cisplatin-5-Fluorouracil (TPF with dose at 60, 60, 600x5 mg/m², respectively) plus cisplatin-based CRT achieved statistically significantly better PFS versus cisplatin-based CRT alone. The Hong Kong NPC-0501 Trial was the only phase III Trial that compared C-CRT versus CRT followed by adjuvant chemotherapy (CRT-C).¹⁸ 803 patients were accrued to this 6-arm trial to explore the therapeutic benefit of changing the chemotherapy sequence, RT fractionation and substitution of 5-fluorouracil (5FU) with capecitabine. The 3-year results showed that changing RT fractionation from conventional to accelerated did not achieve any therapeutic benefit. Among the patients assigned to conventional-fractionation, those given induction cisplatin-capecitabine achieved more favorable PFS compared to those given adjuvant cisplatin/5FU. Moreover, the induction regimen with capecitabine was more convenient and less toxic (less neutropenia and electrolyte disturbance) than that with 5FU.¹⁸

Targeted Therapy

A phase II trial (RTOG 0615) showed that the addition of bevacizumab (anti-vascular endothelial growth factor, VEGF) to cisplatin-based CRT (using IMRT) followed by adjuvant chemotherapy achieved a 2-year distant metastasis-free interval of 90.9% (95% confidence interval [CI] 82.2-99.5) in patients with stage III-IVB disease (n=46); however, the overall 2-year PFS was only 74.7% (95% CI 61.8-87.6).¹⁹ Although two small trials have tested Cetuximab with RT +/- concurrent and sequential chemotherapy, this regimen has never been compared directly with cisplatin-CRT.^{20,21} Based upon these results, consensus is that neither VEGF nor EGFR targeting strategies are of high priority for clinical trial development in NPC. The role of other targeted therapy in NPC is still in early testing. Genomic analysis suggests that the NF- κ B, WNT and PARP pathways may be important in NPC.^{22,23} However, further evidence is warranted prior to embarking upon large scale trials testing these potentially relevant targets.

Immunotherapy

Non-keratinizing EBV⁺ NPC is usually associated with a dense infiltration of tumor stroma by lymphocytes, and therefore is an attractive target for immunotherapy. However, NPC is also notorious for its ability to acquire adaptive resistance to the host's immune surveillance. Previous immunotherapeutic strategies focused on EBV-specific vaccines using dendritic cells or peptides, autologous cytotoxic T-cell therapy and induction of EBV lytic infection. Studies using adoptive transfer of EBV-specific cytotoxic T-cells have shown that this can induce durable immunogenic response, with promising objective responses and sustainable disease control.²⁴⁻²⁷ Recent studies using ICI, primarily targeting the PD1/PD-L1 pathway in the recurrent/metastatic setting have shown promising clinical activity (see below).⁵⁻⁷ There are at least two on-going trials of ICI for locoregionally-advanced NPC. The first is a phase II single-

arm study of CRT +/- adjuvant nivolumab up to 3 months at different dose schedules (NCT03267498). The second is a phase III randomized trial to evaluate 1-year adjuvant camrelizumab after CRT versus observation in stage III-IVA NPC (NCT03427827).

Meeting discussion: Proposed trials in Locoregionally-advanced NPC

Panel members agreed that instead of including all stage III-IVA patients nondiscriminately, the focus should be on the patient subgroups with $\geq 30\%$ failure rate or a 5-year PFS $< 70\%$ as the initial criteria for entry into the proposed trials. Based on modern series of patients who were imaged with MRI and treated with IMRT provided Pan et al., patients with T3N2, T4N1-3 or T1-3N3 (AJCC/UICC staging 8th edition) should be eligible.²⁸ Other prognostic factors worth considering include the primary site gross target volume > 30 cc, lactate dehydrogenase level > 150 , or EBV-DNA > 1500 copies/ml. The trial proposed would include induction chemotherapy with one of the following regimens: modified TPF (as above), cisplatin/capecitabine, cisplatin/5FU, cisplatin/gemcitabine, or cisplatin/paclitaxel. There was consensus that the specific induction regimen can be selected by each participating institution according to its institutional practice. One suggestion is that only patients with detectable EBV-DNA after induction chemotherapy and those with T4N2-3 cancer at diagnosis would be randomized in the next step. This inclusion strategy would allow for enrichment of patients with a very high-risk of recurrence and an estimated 5-year PFS $< 50\%$. The hypothesis is that the addition of ICI, specifically an anti-PD1/PD-L1 antibody, will improve PFS in these very high-risk patients.

Three options were discussed. In the first option, patients would be randomized to CRT alone vs. CRT + anti-PD1/PD-L1 antibody followed by 1-year of adjuvant anti-PD1/PD-L1 antibody (**Figure 1A**). In the second option, patients with detectable EBV-DNA 1 week after completion of the entire treatment course or those with very high-risk (EBV⁺ after induction

chemotherapy or T4N2-3 cancer), would be randomized to 1- year of adjuvant ICI or observation (**Figure 1B**). In the third option, all registered patients would be randomized following induction chemotherapy to CRT plus ICI or CRT alone (**Figure 1C**). Those with detectable EBV-DNA following induction chemotherapy and CRT, together with all T4N2-3 patients, would be included in the second randomization to adjuvant ICI for 1 year or observation. This third hybrid design was the least favored by the group, as the target sample size would be rather large, and results would be hard to interpret. In the first two options, with PFS as the primary endpoint and 2:1 randomization, it would require 316 patients to detect a hazard ratio of 0.70 (alpha 0.05, 80% power) favoring the experimental arm.

Widely-metastatic NPC

An electronic survey was sent out to a subset of the CTPM which focused on patients with widely metastatic disease. This survey was designed to develop an understanding of the current diagnostic and therapeutic landscape of widely-metastatic NPC. The results of that survey demonstrated consensus that a platinum/gemcitabine chemotherapy ‘doublet’ is considered the standard first-line regimen in the recurrent/metastatic setting. In contrast, there was no consensus for maintenance therapy post objective response or disease stabilization in the first-line setting. The choices for second and subsequent lines of therapy were likewise highly variable.

Two anti-PD-1 antibodies, nivolumab (BMS) and pembrolizumab (Merck), have completed single-arm phase II clinical trials in patients with refractory recurrent/metastatic NPC, yielding objective response rates of 20.5% (95% CI 9.8-35.3) and 25.9% (95% CI 11.1-46.3), respectively, one-year PFS of 19.3% (95% CI 10.1-37.2) and 33% , respectively and one-year

OS of 59.0% (95% CI 44.3-78.5) and 63%, respectively.^{5,6} Similarly, an expanded phase I trial reported high activity for camrelizumab (anti-PD1 antibody, Hengrui Medicine) alone as second-line therapy in 93 patients with recurrent/metastatic NPC (not selected for PD-L1 expression) with a response rate of 34% (95% CI 24-44) and 1-year PFS of 27.1% (95% CI 21.4–32.8).⁷ Importantly this study also tested the combination of camrelizumab and cisplatin/gemcitabine as first line therapy in 23 patients with recurrent/metastatic NPC and demonstrated an objective response of 91% (20 of 22 assessable patients, 95% CI 72-97) and a 1-year PFS of 61.4% (95% CI 50.4-72.4).⁷

Clinical trials in widely-metastatic NPC can build on these data to address existent therapeutic gaps and provide opportunities to access novel molecularly targeted and immunotherapeutic agents. Molecular pathways of interest include VEGF and VEGFR, phosphoinositide 3-kinase (PI3K), cyclin dependent kinase (CDK) 4/6, DNA repair and epigenetic targets (e.g. embryonic ectoderm development protein, histone deacetylase), while immuno-oncology armamentaria beyond PD1/L1 blockade such as costimulatory molecules, other ICIs, vaccines and adoptive cell transfer are actively being considered in this disease. Biomarkers that enable differentiation between responders and non-responders and those that offer insights into biological mechanisms of sensitivity and resistance are of top priority.

Meeting discussion: Proposed trials in widely metastatic NPC

Two clinical trial designs were discussed by the group. Design one involves a randomized phase III trial comparing two treatment arms in the first-line treatment of recurrent/metastatic NPC (**Figure 2A**). The main objective is to investigate whether the addition of a PD1/PD-L1 antibody to ‘standard’ first-line chemotherapy could improve treatment outcome. The control arm would be platinum-gemcitabine chemotherapy for 6-8 cycles. The

rationale for selecting this platinum-doublet is based on a phase III study, which found that cisplatin/gemcitabine was superior to cisplatin/5FU in objective response and survival in previously untreated recurrent/metastatic NPC.²⁹ The experimental arm would consist of treatment with the same doublet given concurrently with a PD1/PD-L1 antibody for 6-8 cycles, followed by 1-year maintenance with PD1/PD-L1 antibody. A cross-over design was suggested by some members, allowing the patients in the control arm to receive the PD1/PD-L1 antibody at progression. The basis for combining chemotherapy with PD1 inhibitor is supported by the positive result of the Keynote-189 study in lung cancer,³⁰ and the feasibility of combining PD1/PD-L1 inhibitors with other platinum-doublets in phase I or II trials in lung cancer.^{31,32} The primary endpoint of this proposal is OS with secondary endpoints including PFS, objective response and toxicity. Eligible patients would be randomized in a 1:1 ratio to either arm across multiple centers.

Since clinical response to nivolumab has been reported in patients with PD-L1 negative tumors,⁵ the group felt that positive PD-L1 expression should not be a pre-requisite for enrollment. Instead, a post-hoc stratification of patients according to PD-L1 expression of their archived tumors was suggested, as well as other known prognostic factors such as the number and the site of metastases (e.g. lung-limited metastases versus extra-pulmonary sites, solitary versus multiple, synchronous versus recurrent).^{33,34} This design was favored by most participants because of its potential impact on clinical practice.

The second proposed trial design involves a master protocol framework to concomitantly evaluate multiple regimens using an adaptive design to select the most active ones for further investigation (**Figure 2B**). Examples of treatment arms include various combinations with a PD1/PD-L1 inhibitor as backbone, such as co-administration with molecularly targeted agents or

other immuno-oncology compounds³⁵ ideally supported by available safety data and biological justification for assessment in NPC. Additionally, monotherapy arms with regimens including cancer vaccines or “off-the-shelf” T-cell immunotherapies would also be appropriate for this design if tolerability has been demonstrated. This “umbrella” trial would enroll recurrent/metastatic NPC patients in second or subsequent line setting. The inclusion of PD1/PD-L1 inhibitor naïve patients would focus on a more immunosensitive population, whereas the inclusion of patients already exposed to these agents would evaluate whether ICI resistance can be overcome. Each arm would operate as a single-arm, two-stage, phase II study with a sample size of ~10-20 patients in stage I, and 30-45 patients in total if proceeding to stage II. Objective response rate was deemed to be the most appropriate primary endpoint for such a study. A challenge to the conduct of a master protocol is the need for multiple pharmaceutical sponsors to provide investigational products under a single umbrella-type study.

Recurrent/Oligometastatic NPC

Loco-regional recurrence (LRR)

LRR of NPC occurs in ~10-15% of patients treated with definitive CRT.³⁶⁻³⁸ In the absence of concomitant distant disease, surgery or re-irradiation are established therapeutic options with local control rates of 66-74% and 64-73%, respectively.³⁷⁻⁴² Surgical salvage for local relapse involves resecting the recurrent tumor. Negative surgical margins at salvage resection is the most important predictor for local control in these patients.^{37,43} Therefore, surgical salvage is typically limited to small recurrences (rT1-2) in which obtaining negative margins is likely feasible. In larger tumors (rT3-4) in close proximity to critical structures (e.g. cavernous sinus, brain, carotid artery, optic structures) surgery is seldom indicated. For these

patients, re-irradiation can be offered. In a recent meta-analysis of re-radiation with IMRT, a pooled 5-year local-failure free survival rate of 72% (95% CI 66-78)⁴² was reported; however this was associated with a 33% (95% CI 30-35) rate of grade 5 toxicity (death), leading to an OS of 41% (95% CI 36-47). Generally, re-irradiation requires doses of at least 60 Gy to achieve the best local control; benefit of higher doses is unclear. Given high rates of late toxicity, some advocate a hyper-fractionation approach based on general radiobiologic principles; though studies to support this approach are small and retrospective in nature. The introduction of particle beams (proton, carbon) confers advances in radiation dosimetry and its use has expanded with more centers worldwide. The physical properties of particle therapy permit the delivery of high dose radiation to volumes in close proximity to critical structures with reduced integral dose compared to photon-based therapies.^{44,45} As a result, particle therapy provides opportunities for reduced toxicity in the primary management of locoregionally-advanced NPC, where the tumor is situated next to critical organs (optic structures, brain stem). Further, particle therapy is ideally suited for reirradiation of recurrent NPC after prior full-dose RT.⁴⁶⁻⁴⁸ In one series of 75 recurrent NPC treated with carbon ion therapy, with a median follow-up of 15 months, the 1-year local recurrence-free survival is 86.6% (95% CI 77.8-96.4) and the overall survival is 98.1% (95% CI 94.4-100).⁴⁹ Strikingly, the grade ≥ 3 temporal lobe necrosis rate is only 1.3%. Particle therapy represents an important avenue of active investigation and the increasing availability of this technology may offer additional treatment options for patients who are not candidates for photon-based therapy.

Meeting discussion: Proposed trials in isolated LRR NPC

Though outcomes may be better with novel radiation technologies, there is a critical need to improve toxicity and survival in patients with LRR NPC. Based on the benefits of ICI in

recurrent/metastatic non-NPC squamous cell cancers,^{50,51} NPC,⁷ and locally advanced lung cancer⁵² the addition of ICI to the management of LRR NPC is worthy of study.

The group proposed a phase II clinical trial which would include all patients with locally recurrent NPC planned for re-treatment with curative intent. Patients with nodal relapse would be excluded because this event is relatively rare and there exists additional complexity in managing this condition. Recognizing the known variability of treatment approaches for local recurrence between centers, patients will first receive curative-intent local treatment considered best institutional practice. Then they would be randomized to either adjuvant ICI (likely anti-PD1/PD-L1 antibody) for 4-6 months or observation. Stratification of high-risk features and treatment method would be considered in the randomization process. The study will be designed to detect a clinically relevant improvement of 3-year PFS from 45% to 64% (HR 1.8, power 85%) and is estimated to require ~150 patients (**Figure 3**).

De-novo Oligometastatic NPC

NPC patients with de-novo oligometastases present simultaneously with local disease and limited metastatic burden beyond regional lymph nodes (AJCC M1). These patients pose a clinical dilemma because they may be treated curatively despite the presence of distant disease. Defining this oligometastatic cohort is clinically important, as long-term cancer control may be achieved with aggressive treatments. Tian et al. retrospectively reported that NPC patients with oligometastases (single organ involvement with <6 lesions on imaging) who received potentially curative regimens demonstrated a superior 5-year overall survival of 38.7%, compared to 7% in patients with widely metastatic disease.⁵³ Additionally, case series of oligometastatic NPC patients treated with radical metastatectomy have reported good disease control.^{33,54,55}

A common standard of care in such patients would be to commence with systemic treatment (chemotherapy). In those who achieve a good response to systemic treatment, consolidative therapy to the primary (CRT) and potential oligometastatic deposits (focused RT and/or surgery) is administered. The commonly adopted chemotherapy regime is a platinum doublet such as cisplatin/5FU or cisplatin/gemcitabine.⁵⁶ The TPF triplet regime can also be used in patients with excellent performance status. Despite these approaches, most patients will succumb to their cancer; therefore, the addition of ICI to this treatment paradigm is worthy of study.

Meeting discussion: Proposed trials in de-novo oligometastatic NPC

In the proposed phase 2 trial, oligometastatic spread would be defined as presence of ≤ 3 metastatic lesions within 2 organs with a maximum size of any metastasis limited to 5 cm. This definition is proposed in order to select patients who are more likely to benefit from an aggressive approach. Patients would receive 3-6 cycles of chemotherapy according to best institutional practice limited to one of three above regimens. Patients with progressive disease on chemotherapy would be taken off study and treated according to the standard of care of the individual institution. Non-responders are uncommon and comprise <10% of these patients. Patients with stable or responding disease would be randomized to either cisplatin-based CRT to the primary site versus the same with concurrent and adjuvant ICI. Oligometastatic deposits will be managed according to best institutional practice, typically focused RT and/or surgery. The primary endpoint will be PFS. Secondary endpoints will include quality of life, toxicities and immune correlative studies. The study will be designed to detect a clinically relevant improvement of 3-year PFS from 35% to 55% (HR 1.8, power 85%) and require ~120 patients (Figure 4).

Correlative biomarkers

Each proposed study will include pre-specified analysis of biomarkers widely used in immuno-oncology (IO), namely PD-L1 status and tumor mutation burden, as well as a broader set of biomarkers for exploratory analysis.^{35,57} PD-L1 assessment (on immune and tumor cells) will be correlated with clinical outcomes at pre-defined cut-points (>1%, >20%, and >50%).^{58,59} Tumor mutation burden will be explored using tertiles of mutation load.⁶⁰⁻⁶² Whether NPC depends on mutation-derived neo-antigens or viral antigens for immune recognition remains unclear; however in HPV-associated malignancies, mutation-based antigens play an important role in predicting ICI response in addition to virally-derived antigens.^{63,64}

For NPC specific biomarkers, circulating EBV-DNA will be measured serially during therapy. A prior study suggested that the dynamic change of circulating EBV-DNA, specifically its detectability after one month of camrelizumab/cisplatin/gemcitabine, highly correlated with survival in recurrent/metastatic NPC receiving this regimen.⁷ Likewise, early changes in ctDNA in other cancers have correlated with long-term outcomes to anti-PD1 therapy and if reproduced in NPC, it may help guide future combination IO strategies.^{65,66}

In addition to these well-known markers, more comprehensive exploratory analysis will be conducted on materials collected in these trials to generate hypotheses on mechanisms of response, innate resistance, and adaptive resistance to ICI in NPC. We have previously provided a comprehensive list of IO biomarkers in head and neck cancers, including those from the tumor, peripheral blood, stool, saliva or imaging studies in the written summary of our CTPM on Immunotherapy of Head and Neck Cancer.³⁵ In patients with sufficient material, we will perform comprehensive genomic analysis including whole exome and transcriptome sequencing and

explore the relationship between immune-related RNA-seq signatures (e.g. interferon-gamma), intra-tumor heterogeneity, and evaluation of the HLA-locus and associated genes.^{61,67-69}

Interestingly, the HLA-locus, which is one of the strongest hereditary risk factors for NPC, has been shown to undergo selection during tumor evolution and associate with response to anti-PD1 therapy.^{68,70,71} Peripheral mononuclear cells could be obtained for immune-phenotyping and assessment of viral-antigen reactive T-cells trajectory over therapy.⁷² The international nature of these trials will provide unique insights into the interaction of the gut microbiome and therapy response. Proposed imaging biomarkers including radiomic analysis of positron emission tomography (PET), CT and MRI scans that can identify immune infiltration in metastatic deposits.⁷³ A subset of patients will be consented for on-therapy biopsies which will permit evaluation of immunologic pharmaco-dynamic markers of treatment response using genomic techniques and multi-parametric histopathology.⁷⁴ The goal of these exploratory studies will be to generate hypotheses to validate in the next generation of immunotherapy trials in NPC and provide insights into possible rational combination therapeutics.

Meeting updates:

Since the meeting, several randomized trials have been either activated or under intensive planning by large institution or group participants. These include: a phase III randomized trial to evaluate 1-year of adjuvant camrelizumab vs. observation after CRT in stage III-IVA NPC (NCT03427827, Cancer Center of Sun-Yat Sen University [CCSYSU], Guangzhou, China), a phase III trial of cisplatin/gemcitabine chemotherapy vs. cisplatin/gemcitabine plus camrelizumab as the first line treatment in recurrent/metastatic NPC (NCT03707509, CCSYSU), and a phase III randomized trial of cisplatin/gemcitabine chemotherapy vs. cisplatin/gemcitabine

plus nivolumab as the first line treatment in patients with recurrent/metastatic NPC (under planning). The last trial will be conducted through NRG Oncology, which has several full and affiliated members in Asia that are actively accruing to the phase III trial in locoregionally-advanced NPC (HN001); it is expected that these sites will accrue to this planned trial.

Conclusions

This CTPM had participation of investigators from different continents to design the future treatment roadmap in NPC. It is well-known that NPC, similar to other virally-driven cancer, is notorious for its ability to cloak the host's immune system and is a good target for immunotherapy. However, until now, there has been no well-coordinated strategy of applying ICI to this cancer. Several exciting trial concepts emerged from this meeting with great enthusiasm of the investigators to move some of these concepts forward, either through the National Clinical Trial Network in North America or other national/international groups in Asia, or both. Success of these trials will depend on industry support and global collaboration of the different clinical trial groups and centers, an initiative that is led by the Head and Neck Cancer Intergroup, supported by the global office of the NCI.⁷⁵

Notes

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List of all invited participants in the NPC Clinical Trial Planning Meeting

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Authors' Disclosures of Potential Conflicts of Interest

Brigitte Ma's COI are directly related to this manuscript. Advisory board: BMS, MSD, Novartis,

Research grant: Novartis, Speaker's honorarium: Roche

Quynh Thu Le: Advisory Board: Genentech & GRAIL, Stock: Aldea.

Brian O'Sullivan: Advisory Board: Merck

Nancy Lee: Advisory Board: Merck, Pfizer, Merck Serono, and Sanofi Aventis, Stock: Astra Zeneca

Brigitte Ma: Advisory Board: Bristol-Myers Squibb, MSD, Novartis, Research Grant: Novartis, Speaker's Honorarium: Roche

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Nadeem Riaz: Speakers Bureau: Illumina; Research Support: Pfizer & Bristol-Myers Squibb

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Figure legends

Figure 1: Proposed randomized phase III trial schemas for very-high risk patients (predicted 5-year progression-free survival <50%) with locoregionally-advanced NPC.

- A. First option
- B. Second option
- C. Third option

Abbreviations: TNM: TNM stage; PFS: progression-free survival; CCRT: cisplatin-based concurrent chemoradiation; IO: immunotherapy including PD1 or PD-L1 inhibitor

Figure 2: Proposed trial designs for patient with widely metastatic NPC

- A. Proposed randomized phase III trial of chemotherapy with or without PD1 or PD-L1 inhibitor in the first-line treatment of recurrent/metastatic NPC patients. (* Denotes optional design, i.e. cross over from arm A to arm B and placebo control are optional.)
- B. Proposed “umbrella” design of randomized phase II trial of PD1 or PD-L1 inhibitor-based doublet with a novel agent in the second or subsequent line treatment of recurrent/metastatic NPC patients.

Abbreviations: IO: immunotherapy including PD1 or PD-L1 inhibitor

Figure 3: Proposed randomized phase II trial of adjuvant immunotherapy following salvage treatment for locally recurrent NPC

Abbreviations: IO: immunotherapy including PD1 or PD-L1 inhibitor

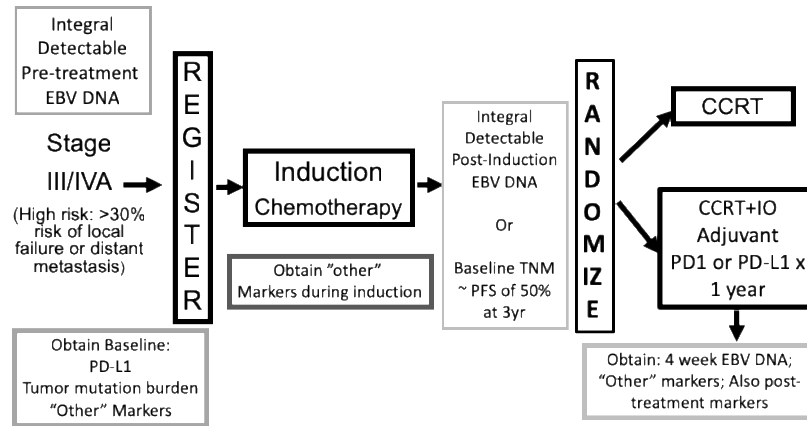
Figure 4: Proposed randomized phase II trial in treating de-novo oligometastatic NPC patients

(* Cisplatin/5FU or cisplatin/gemcitabine or paclitaxel/cisplatin/5FU in good performance status patient; **Cisplatin based concurrent chemotherapy; *** Disease progression expected in <10% of the patients)

Abbreviations: IO: immunotherapy including PD1 or PD-L1 inhibitor; CCRT: cisplatin-based concurrent chemoradiation.

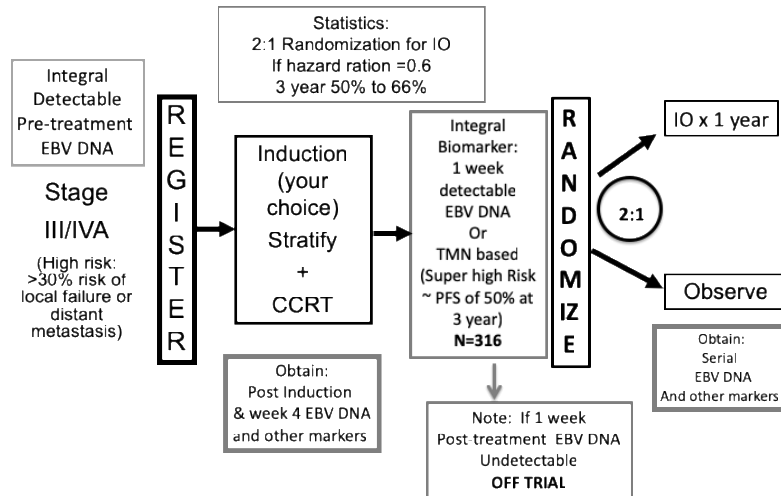
Figure 1
A

NPC Trial Proposal 1 (Induction)



B

NPC Trial Proposal 2 (Adjuvant)



C

NPC Trial Proposal 3 (Hybrid Design)

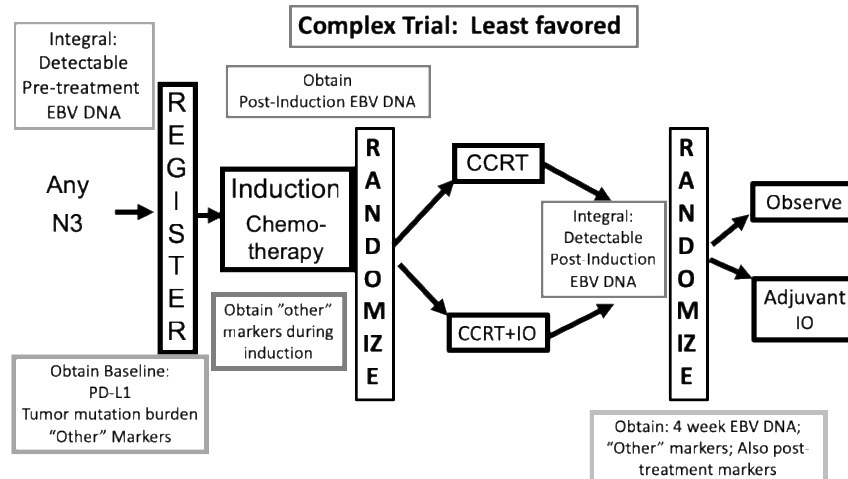
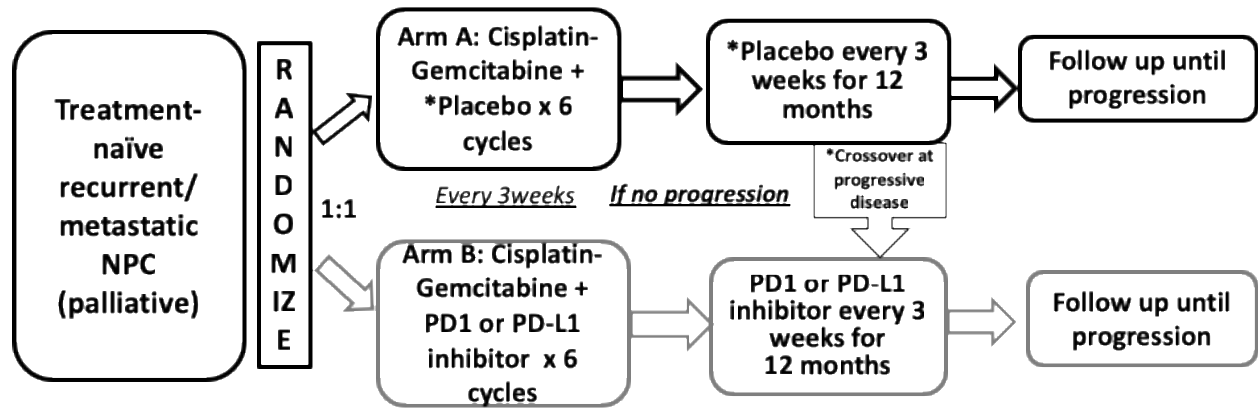


Figure 2

A

Design 1: Randomized phase III study of chemotherapy with or without PD1/PD-L1 inhibitor in first-line treatment of recurrent/ metastatic nasopharyngeal carcinoma



B

Design 2: Umbrella design – randomized phase II study of PD1 or PD-L1 inhibitor-based doublet with novel agents in multiply pre-treated recurrent/ metastatic nasopharyngeal carcinoma (NPC)

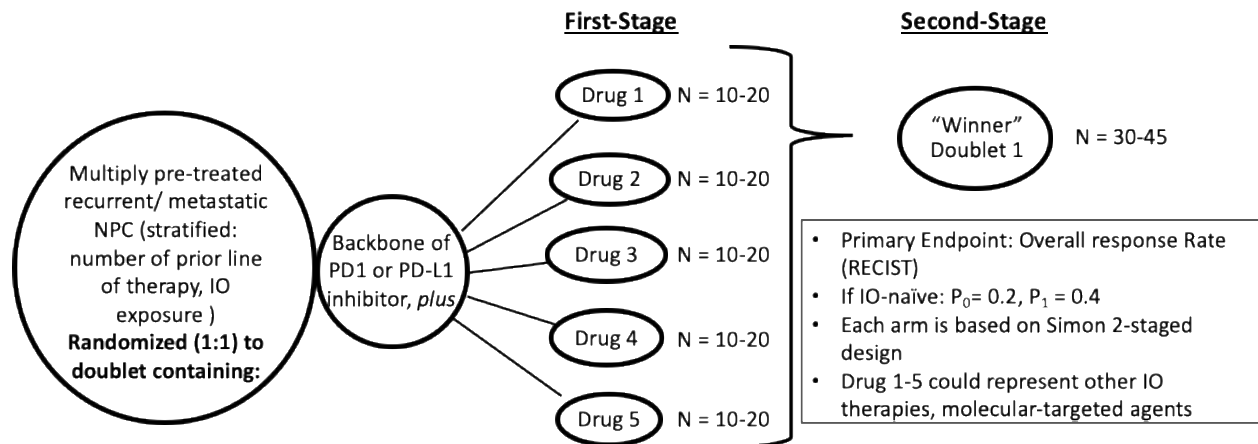


Figure 3

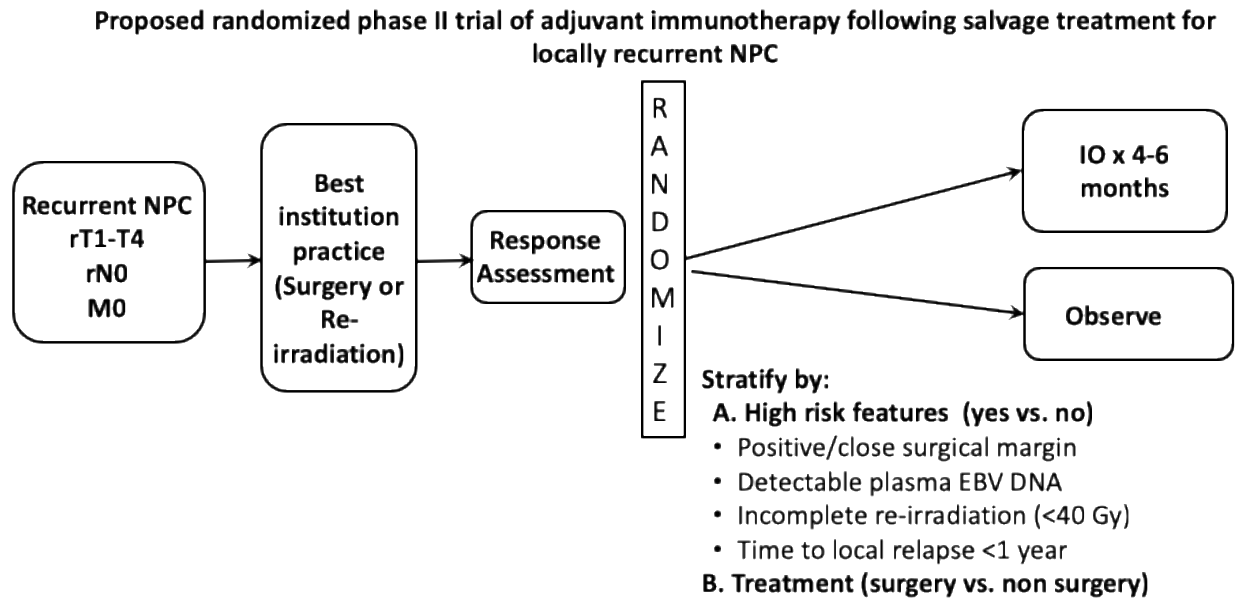


Figure 4

