Head and Neck Cancer Steering Committee

Naso-Pharyngeal Cancer Clinical Trials Planning Meeting

January 27-28, 2018, Phoenix, AZ

A. Dimitrios Colevas, M.D., Quynh Thu Le, M.D., Brian O'Sullivan, M.D.

with Shakun Malik, M.D.

Introduction/ Meeting Description

The Previously Untreated Locally Advanced Task Force of the Head and Neck Cancer Steering Committee proposed a Clinical Trials Planning Meeting on Nasopharyngeal Cancer (NPC) that was approved by the NCI in January 2017. The meeting was held in Phoenix, AZ on January 27-28, 2018.

Background/Importance of Research Topic/Disease/Limitations

- Nasopharyngeal carcinoma is an enigmatic malignancy, which exhibits marked racial and geographical differences.
- Worldwide, the incidence of NPC is approximately 51,540 for 2018 https://www.uptodate.com/contents/epidemiology-etiology-and-diagnosis-of-nasopharyngeal-carcinoma and the mortality rate is anticipated to be 10,030. Nasopharyngeal cancer is, however, much more common in certain parts of Asia and North Africa, particularly in southern China. It is also more common among Inuits of Alaska and Canada, and among some immigrant groups in the United States, such as recent Chinese and Hmong immigrants.
- The risk of NPC increases slowly throughout life, but it can occur in people of any age, including children. About half of the people with NPC in the United States are younger than 55 years old.
- Overall survival (OS) for patients with NPC in the US and worldwide remains sub-optimal. Population-based studies have demonstrated five-year OS rates for Asians to be approximately 63% and approximately 47% for Non-Hispanic whites. (7) Even for patients with localized disease, there is room for improvement. The five-year OS rates of the above two populations with localized disease is 84% and 62%, respectively. For patients with metastatic disease, five-year OS is 22-34%.
- The standard treatment for patients with localized or locoregional (not spread beyond the head and neck region) is external beam radiation therapy, with concurrent systemic therapy for patients with advanced local or locoregional spread. The present standard regimen of concomitant cisplatin with radiation followed by adjuvant cisplatin and 5- fluorouracil (5-FU) was established in 1998 when a randomized control trial (RCT) demonstrated a survival advantage associated with the addition of systemic therapy to radiation.
- The development of more conformal radiation techniques such as intensity modulated radiation therapy (IMRT) has been associated with a dramatic

increase in local control to the point where patients presenting with locoregional disease are able to achieve a long term local control rate of up to 95% with a concomitant reduction in adverse events.

- Unfortunately, progress in the 17 years since the US intergroup study with respect to systemic treatment has been more modest, with distant relapse approximating 20% in most studies, and virtually none of these patients are cured following systemic relapse.
- In the metastatic setting, while single agent chemotherapy is associated with response rates of 15-30 % with such agents as cisplatin, taxanes, 5-FU and gemcitabine and combination doublets of these agents in the 30-60% range, responses are at a significant price of toxicity and typically not durable.
- Therefore, there is a significant need for both more effective and less toxic treatments for patients with either locoregional or metastatic NPC.

Invited attendees included medical oncologists, radiation oncologists, surgeons, immunologists, translational researchers, statisticians and industry partners with agents focusing on nasopharyngeal cancer.

The planning team and breakout groups were charged to focus on optimal strategies for incorporation of immunological agents such as immune checkpoint inhibitors (e.g., anti-CTLA-4 and anti-PD-1 antibodies) into definitive chemo-radiation treatment of NPC. Use of blood EBV DNA testing and molecularly targeted agents will also be incorporated in these next generation of trials.

In addition, the group was to explore possibility of potential clinical trials with cellular-based treatments as part of definitive multi-modality treatment to include chimeric antigen receptor (CAR) and T cell receptor (TCR) strategies, as these are specifically relevant in virally associated cancers such as NPC and proof of concept trials in this area related to EBV associated cancers was also discussed.

The purpose of this meeting was:

- To develop 2-3 clinical trials to study the most promising immunotherapies in the treatment of NPC with or without radiation and or chemotherapeutic agents feasible through National Cancer Trials Network (NCTN).

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The first segment of the meeting focused on:

- Understanding the state of the science of the biology behind the association between EBV and NPC. Specifically, what molecular and immunological issues relating to EBV might be used to develop better NPC treatments?
- Review of the present state of preclinical and translational NPC research with a focus on what is ready to move into definitive clinical study and what gaps remain to be closed to move promising work forward.
- Review the present progress of early and phase II/III trials that relate generally to EBV and cancer, and specifically to EBV in NPC.
- Develop a framework for prioritization of efforts on the basic science, translational and clinical trial level with respect to knowledge and tools needed to move forward with implementation of an optimized clinical trial portfolio focusing on NPC. This would include issues concerning biomarker assay development, testing, validation, clinical endpoint selection and patient population prioritization.
- Develop a research agenda to include Phase I-Phase III evaluation of agents that target molecularly defined pathways in combination with standard chemotherapy in nasopharyngeal carcinoma and for translational directions to further advance knowledge in NPC.
- Publication of findings in a peer-reviewed journal.

During the second half of the meeting, CTPM Leaders had the participants break out into 3 Working Groups. Each breakout group were tasked to develop 2-3 potential concepts that were discussed at the face to face meeting and then prioritized for development. Breakout groups had met at least twice a month for 6 months prior to the meeting.

- Local Regional NPC -Leaders: Anne Lee & Nancy Lee
- Recurrent Oligometastatic NPC- Leaders: John Waldron & Chwee Ming Lim
- Widely Metastatic NPC- Leaders: Brigette Ma & Lillian Siu

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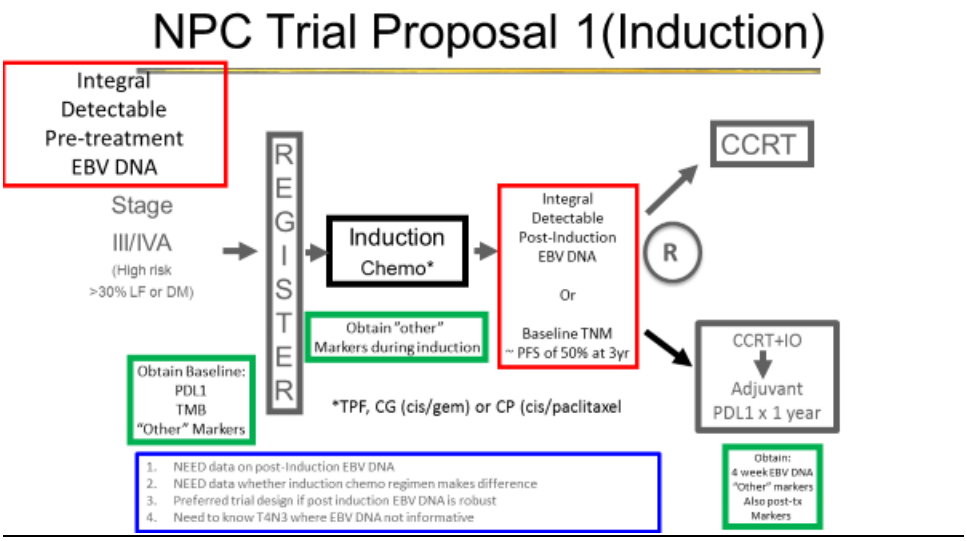
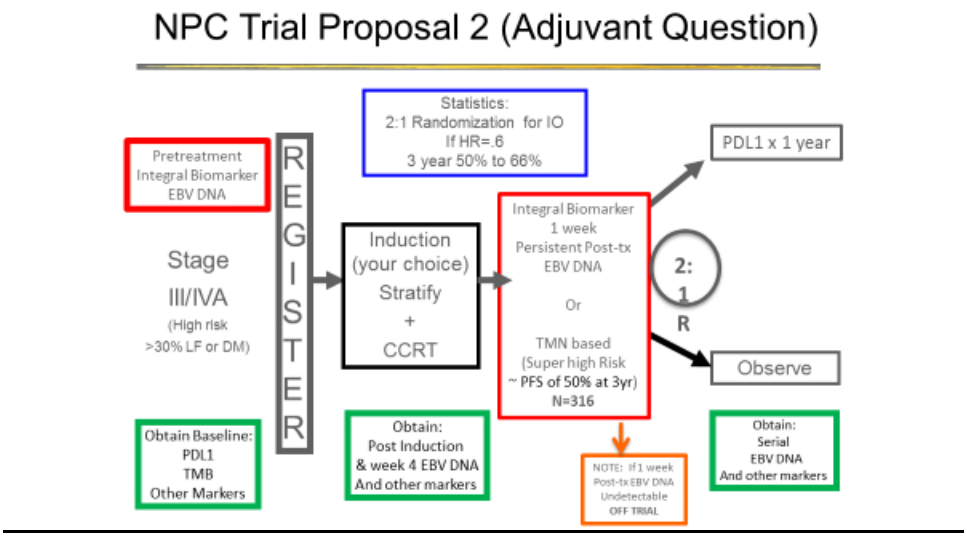
Proposals discussed during the meeting:

Local Regional Breakout Group





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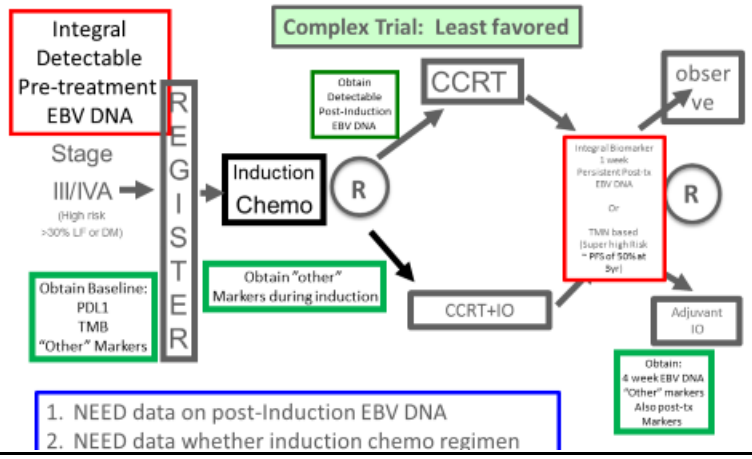
Induction Regimens (Declared upfront)

TPF: 3 cycles of docetaxel, cisplatin and continuous intravenous 5FU every 3 weeks

GP: 3 cycles of Gemcitabine + Cisplatin

PT: 3 cycles of Cisplatin + Paclitaxel

NPC Trial Proposal 3 (Hybrid Design)



Recurrent

Legend: Red -Required by Protocol
Green – Correlatives
Blue – Questions that need answers

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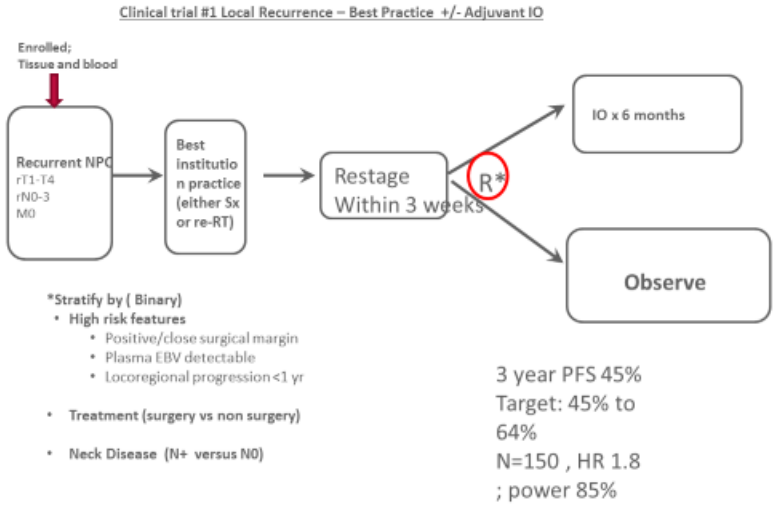
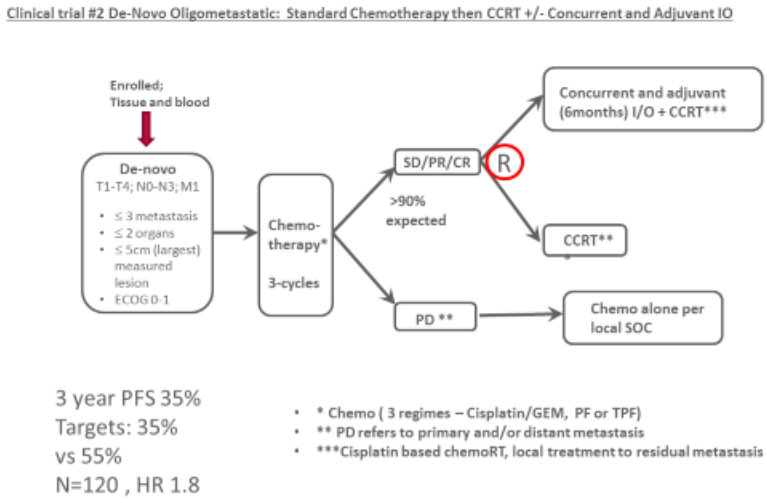
Oligometastatic Breakout Group:





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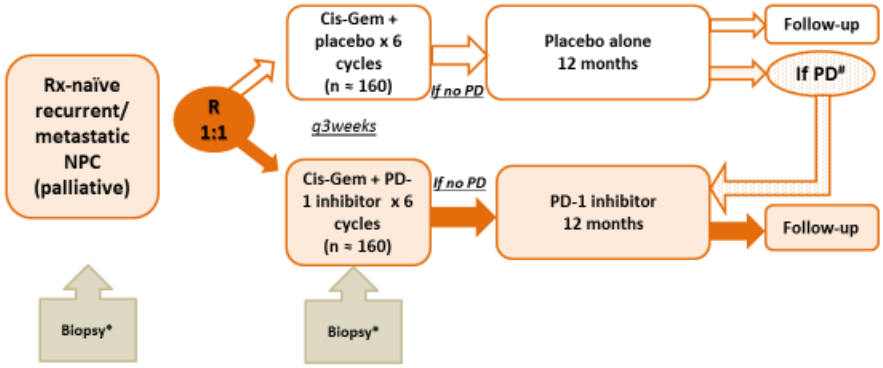
Widely Metastatic Breakout Group:

Schema – 1st line W/M NPC: 1-yr OS as endpoint



- Primary endpoint: 1-yr OS. Assume 15% difference from 75% to 83% OS at 1-yr, N = 320 (assume HR=1.54, 80% power)
- Secondary: ORR (RECIST), PFS, toxicity, correlative endpoints.
- Exclusion: prior exposure to CTL, vaccine, checkpoint inhibitors.
- Mandatory: Archived FFPE tissues (adequate no. of slides +/- not older than predefined age).
- *Optional: 10-15% (n = 30-45) of pts from dedicated centers will undergo fresh biopsy at baseline, +/- on treatment (prior to cycle X) for 'deep-dive' exploratory biomarkers
- Stratification: lung-only mets; PD-L1 expression in archived specimens.
- Biomarkers: mandatory (central lab) – PD-L1, HLA genotyping, pEBV DNA. Opt: RNAseq, nanostring, immunophenotype, NGS.
- #Crossover design for eligible patients

Sample size calculation - background

- Control arm: cisplatin-gemcitabine for 6 cycles. Based on paper by Mainland China Zhang et al (Lancet 2016), 1-yr OS (off the curve) around 75-80%), 1-yr PFS 20%, ORR 64%. In a single-arm study of cis-gem by Hong Kong investigators who allowed pts to have chemo until PD (Ngan 2002), the 1-yr OS was 62%. So, 1-yr OS of around 71-75% is realistic.
- Experimental arm: no NPC data for the triplet, nivolumab has activity in subsequent arm. Safety of cis-gem + nivolumab has been evaluated in lung (Rivzi et al, Lancet Oncol).
- Usual practice after failing 1st line: Variable in Asia. Some may use local ablative therapies (e.g. SBRT, RFA)
- PD-1 inhibitors generally not reimbursed in most Asian countries.

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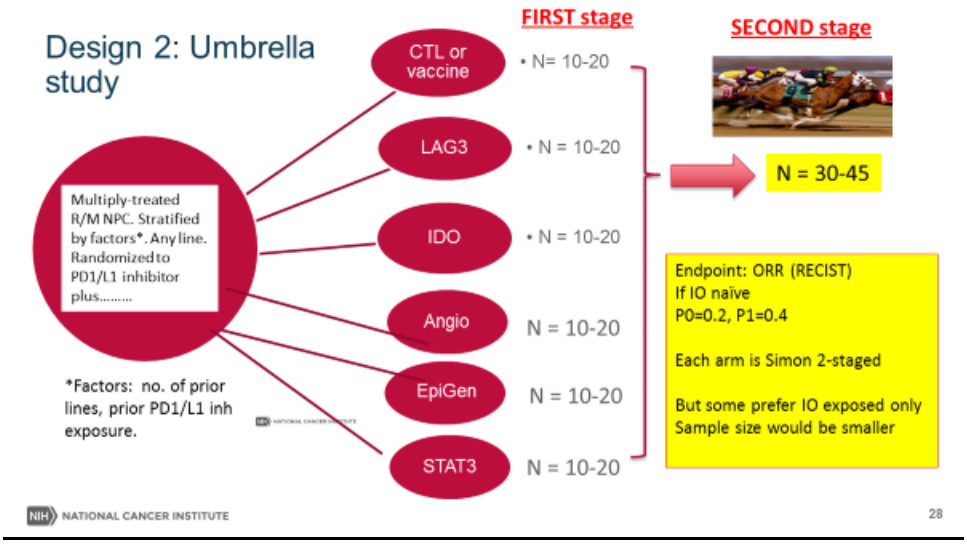

The six agents chosen to combine with a PD-L1 are "straw men" and most likely will be updated and/or replaced in design as more information is learned about these and other immunotherapy targets and agents.

Anticipated Consensus & Recommendations Action(s)

- ECOG-ACRIN and NRG Head and Neck Cancer Disease Committees will prioritize which concepts that will move forward.
- Publication of the outcome of meeting

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Names of Attendees at Meeting & their Affiliation

This was the first international CTPM.

***Planning Team Members**:*

Anne Wing-Mui Lee – University of Hong Kong, Hong Kong

Brigette Ma – Chinese University, Hong Kong

Chwee Ming Lim– National University of Singapore, Singapore

Jun Ma – Sun Yat Sen University, China

Nancy Lee – Memorial Sloan Kettering Cancer Center, New York, USA

Local Regional Group:

North America/ UK/ Europe
Nancy Lee
Barbara Burtness
Minh Truong
Brian O'Sullivan
Allan Hildesheim
Benjamin Pinsky
John "Drew" Ridge

Asia-Pacific

Anne Lee
Anthony Chan
Chaosu Hu
Jianji Pan
Joseph Chang
Jun Ma
Wan-Teck Darren Lim

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Bob Ferris
Maura Gillison

Locally Recurrent Oligometastatic
North America/ UK/ Europe

John Waldron
Boris Freidlin
Quynh Le
Nadeem Riaz
Minh Truong
Fei-Fei Liu

Asia-Pacific

Chwee Ming Lim
Dora Kwong
Brigette Ma
Jun Ma
Chaosu Hu

Widely Metastatic
North America/UK/Europe

Lillian Siu
Ezra Cohen
Dimitri Colevas
Robert Ferris
Priscilla Goncalves
Steven Gottschalk
Fairooz Kabbinavar
Quynh Le
Shuli Li
Troy Messick
Lawrence Young

Asia-Pacific

Brigette Ma
Rajiv Khanna
Jin-Ching Lin
Kwok Wai Lo
Maria Lung
Corey Smith
George Tsao
Li Zhang

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Clinical Trial Meeting Agenda

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12:30 PM	Welcome & Logistics	Quynh Thu Le, M.D. Dimitri Colevas, M.D. Brian O'Sullivan, M.D.
12:45 PM	**Landscape of NPC- Current Treatments**: Multimodality, Loco-Regional Disease Textbook: how do we treat this now How to follow, staging, etc. Advanced Recurrent, Systemic NPC	 Anne Lee Brigitte Ma
1:25 PM	**State of the Art Clinical Trials – Immunology, Vaccine, Cell therapy, Checkpoint Inhibitors** Multimodality, Loco-Regional Patients Recurrent, Metastatic-NPC - Targets beyond PD-L1, PD-1, anti-CTLA-4	 Jun Ma Lillian Siu
2:05 PM	**Immunology – EBV-What is Important for Clinical Translation** EBV biology: Relevance to nasopharyngeal cancer pathophysiology—	 Lawrence Young
2:20 PM	Genomics & Novel Targeted Pathways	Kwok Wai Lo
2:40 PM	Viracta Therapeutics	Marshelle Warren
2:45 PM	Atara Biotherapeutics	Akshay Sudhindra
2:50 PM	Discussion	
3:10 PM	Break (on your own)	

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3:30 PM	Current Biomarkers for NPC, EBV and other Biomarkers in Cellular Immunotherapy	
	CDP Diagnostic Biomarker Development	Kelly Kim
	Biomarkers for ImmunoOncology	Nadeem Riaz
4:10 PM	Discussion	
4:20 PM	Breakout Groups Meet	
	Breakout Group 1 – Local Regional Disease: Breakout Leaders- Anne Lee, Nancy Lee	
	Breakout Group 2 – Widely Metastatic Disease Breakout Leaders: Brigitte Ma and Lillian Siu	
	Breakout Group 3: Local regional- Oligo-Metastatic Breakout Leaders: John Waldron and Chwee Ming Lim	
6:00 PM	Adjourn	

Day 2 – Sunday, January 28, 2018

8:00 AM	Recap of Day 1 – Co-Chairs of Meeting - Dimitri Colevas, Quynh Thu Le, Brian O'Sullivan
8:30 AM	Breakout Groups meet
10:00 AM	Break (on your own)
10:20 AM	General Session – Breakout Groups Report Out
11:30 AM	Adjourn General Meeting
11:45 AM	Executive Session
12:30 PM	Adjourn Executive Session

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- *This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.*