Head & Neck Cancer Steering Committee
Immunotherapy in Head & Neck Cancer
Clinical Trials Planning Meeting
November 9-10, 2014
FAES Education Center, Building 10, NIH Campus
Bethesda, M.D.
Co-Chairs
Julie Bauman, M.D., MPH, Ezra Cohen, M.D., Robert Ferris, M.D., Ph.D.

Introduction/Meeting Description:

Recent advances in the treatment of other diseases with immunotherapeutic agents have led researchers to begin exploring Head & Neck Squamous Cell Carcinomas (HNSCC) as ideal models for clinical trials incorporating immunotherapy in cancer treatment due to their unique biology and clinical characteristics:

- HNSCCs, although frequently initiated by known carcinogen exposure, are immunosuppressive malignancies in which specific, targetable immune escape mechanisms have been elucidated. Antagonists to inhibitors of immune response that lead to clinically significant immune activation, irrespective of the tumor type, are now available commercially and some are FDA approved treatments, e.g., anti-CTLA-4 and anti-PD-1 monoclonal antibodies .
- HNSCCs often develop in accessible anatomical locations, allowing for serial tumor tissue samples. Ability to do serial biopsies of tumors under treatment with immunotherapy will deepen the understanding of immune targets and mechanisms, knowledge that will be applicable to the field of oncology broadly.
- Human papillomavirus (HPV)-associated oropharyngeal SCC is a model of virally-induced cancer, presenting the opportunity for tumor-targeted, antigen-specific treatment. Presence of specific tumor antigens (TAs) in HPV + HNSCC, e.g. E6 and E7 oncoproteins, raises the possibility of precise TA-targeting and immune monitoring. Immunotherapy may lead to rational de-intensification strategies which can preserve the high cure rate while sparing late treatment toxicity.

Currently available treatment options for HNSCCs consist of surgery, radiation and chemotherapy, administered in single or multi-modality regimens; however, the overall treatment efficacy still needs large improvements. Substantial clinical gains from further intensification or other variations using only these three modalities are unlikely. Fortunately, immunotherapy has emerged as a highly promising fourth treatment modality in treatment of cancer, and its incorporation into HNSCC treatment led to the development of this Clinical Trial Planning Meeting.

Invited attendees included surgeons, medical oncologists, radiation oncologists, immunologists, radiologists, pathologists and patient advocates.

The purpose of this meeting was to:

1. Survey the available and in-development immunotherapies which specifically target the mechanisms of immune evasion in HNSCCs, both carcinogen and HPV related cancers
2. Review and understand the special considerations for conducting immunotherapy trials in HNSCC
3. Design three priority NCTN phase II/III trials which will rationally integrate immunotherapy into previously untreated and recurrent and metastatic HNSCC population and HPV (+) SCC population.
4. Explore unique endpoints and study design issues likely to be encountered in the HNSCCC immunotherapy trials
5. Identify biomarkers of immunotherapy response discovery and validation

Background/Importance of Research Topic/Disease Limitations:

Access to clinical trials incorporating novel immunotherapies is extremely limited for both HPV (+) and HPV (-) HNSCCs. The HNSC recognizes a compelling opportunity to highlight HNSCC as a model epithelial malignancy for the investigation of immunotherapy, the “fourth modality.” A significant collateral benefit from this effort will be a mechanistic, tissue-

based understanding of tested immunotherapies in a model cancer which includes both viral and carcinogen-induced subtypes.

The CTPM provided the opportunity to explore the development of concepts with immunotherapy agents for treatment of HNSCCs to include:

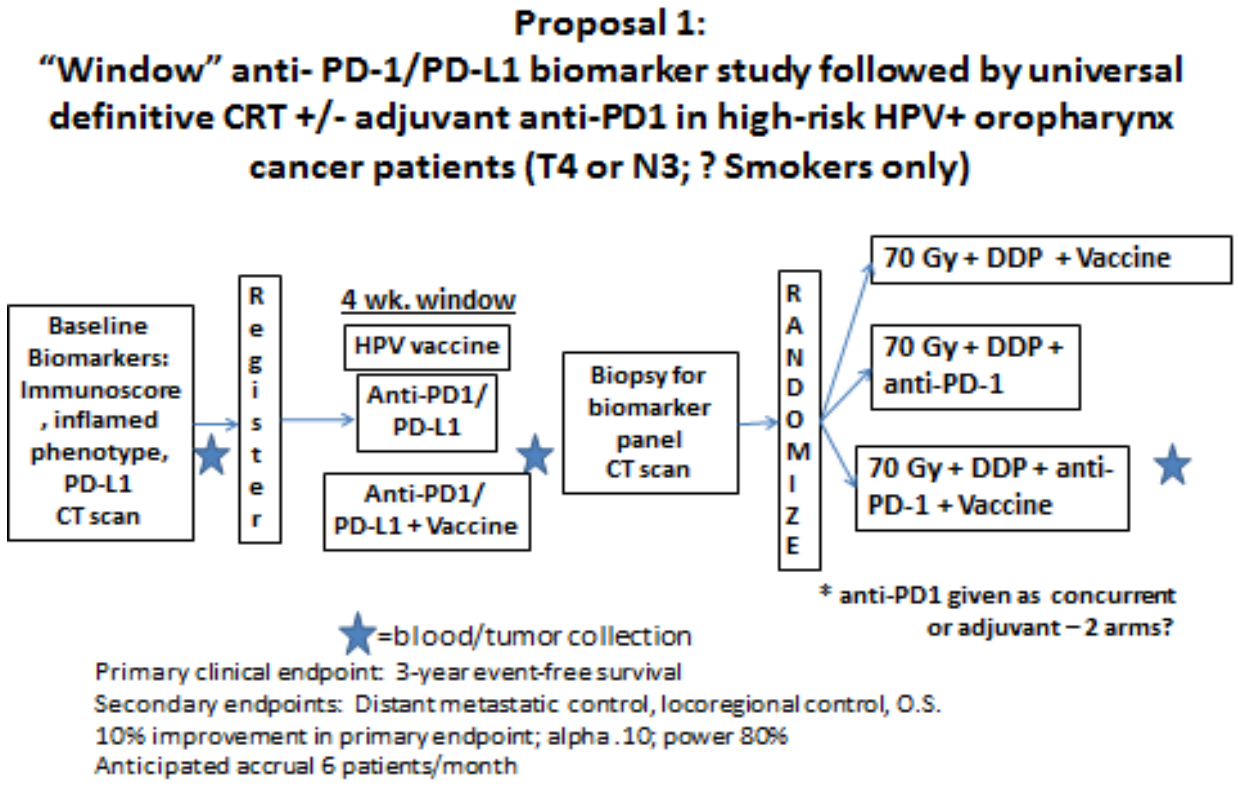
- Identifying the optimal therapeutic targets in HNSCCs;
- Keeping in view the treatments already approved or in development commercially;
- Using the national expertise in immunology and immunotherapy, and HNSCC expertise;
- Focus on clinical trial designs that will include tumor tissue collection and biomarker incorporation.

Consensus & Recommendations:

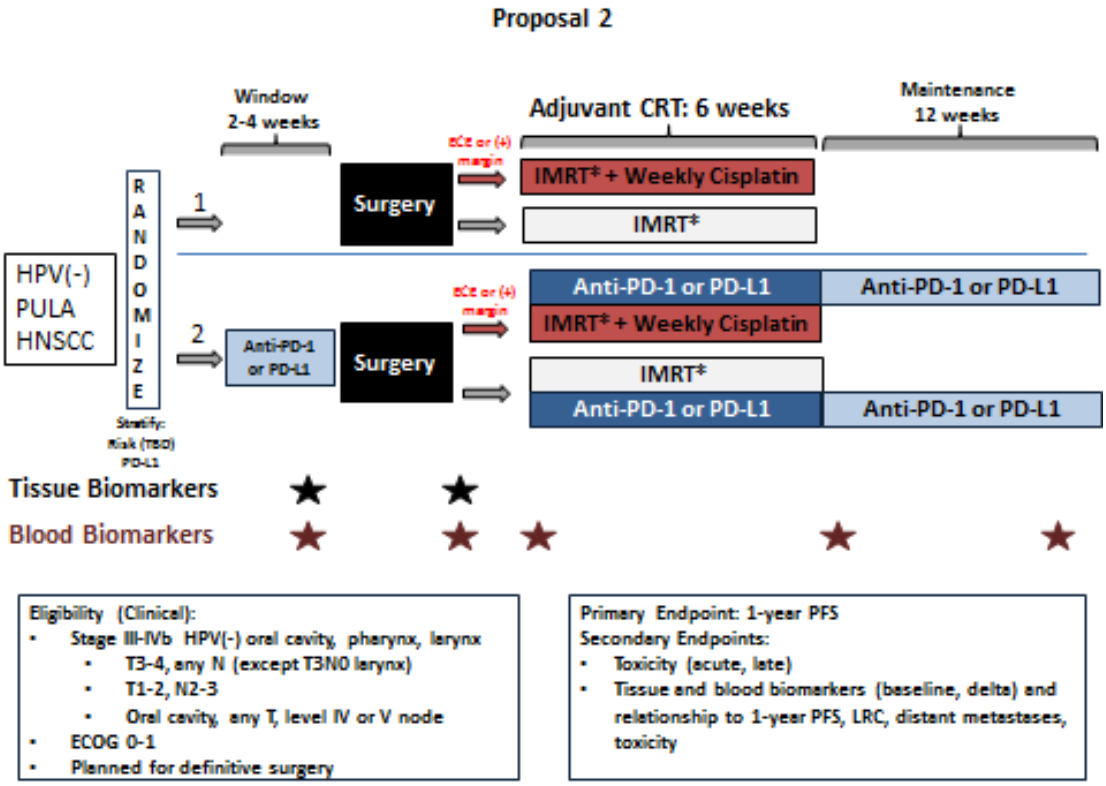
The CTPM Leaders had the participants break **out** into 4 Working Groups:

1. Best Agent(s) and Trial Design in HPV+ PULA Disease
2. Best Agent (s) and Trial Design in HPV – PULA Disease
3. Best Agent (s) and Trial Design in Recurrent/Metastatic Disease
4. Monitoring for Efficacy in Immunotherapeutic Trials –Specimen Analyses, Imaging, Correlative Immune Monitoring

<u>Recommendation from Group1 – Previously untreated Locally Advanced (PULA) HPV+ HNSCC</u>

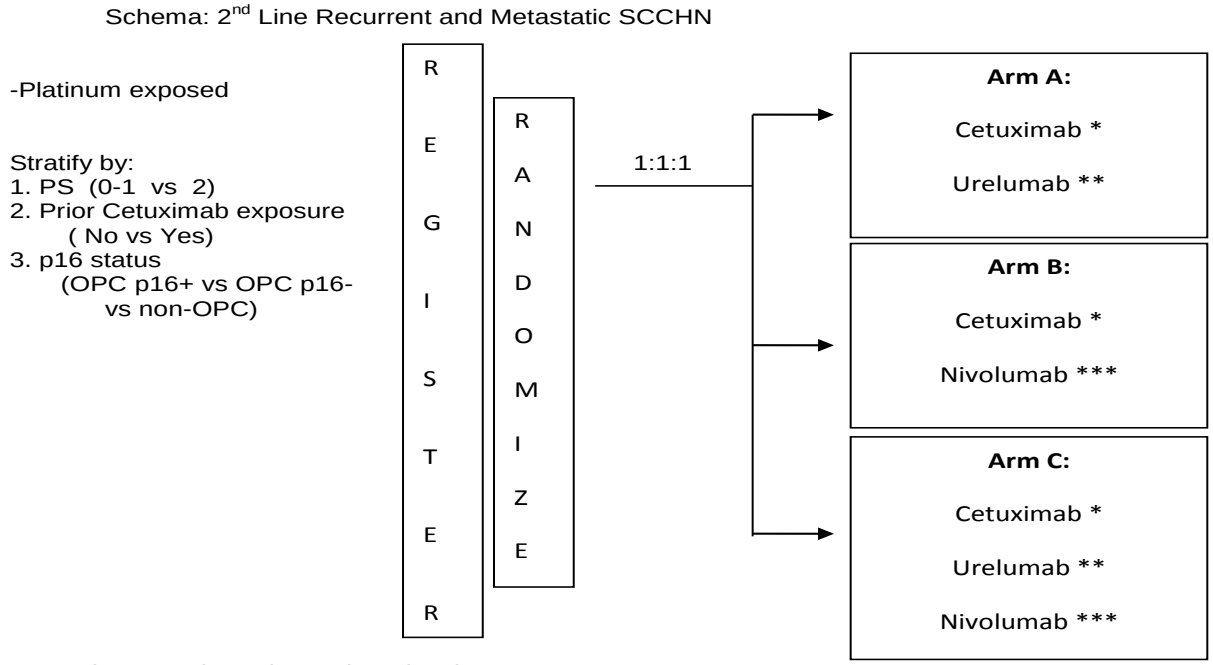


Recommendation from Group 2 - Previously untreated Locally Advanced (PULA) HPV-negative HNSCC



Recommendations from Group 3 – Recurrent/Metastatic HNSCC

1. Schema: 2nd Line Recurrent and Metastatic SCCHN – ECOG in development and proposed to BMS



Accrual: 120 patients (40 patients/arm)

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1 cycle = 28 days

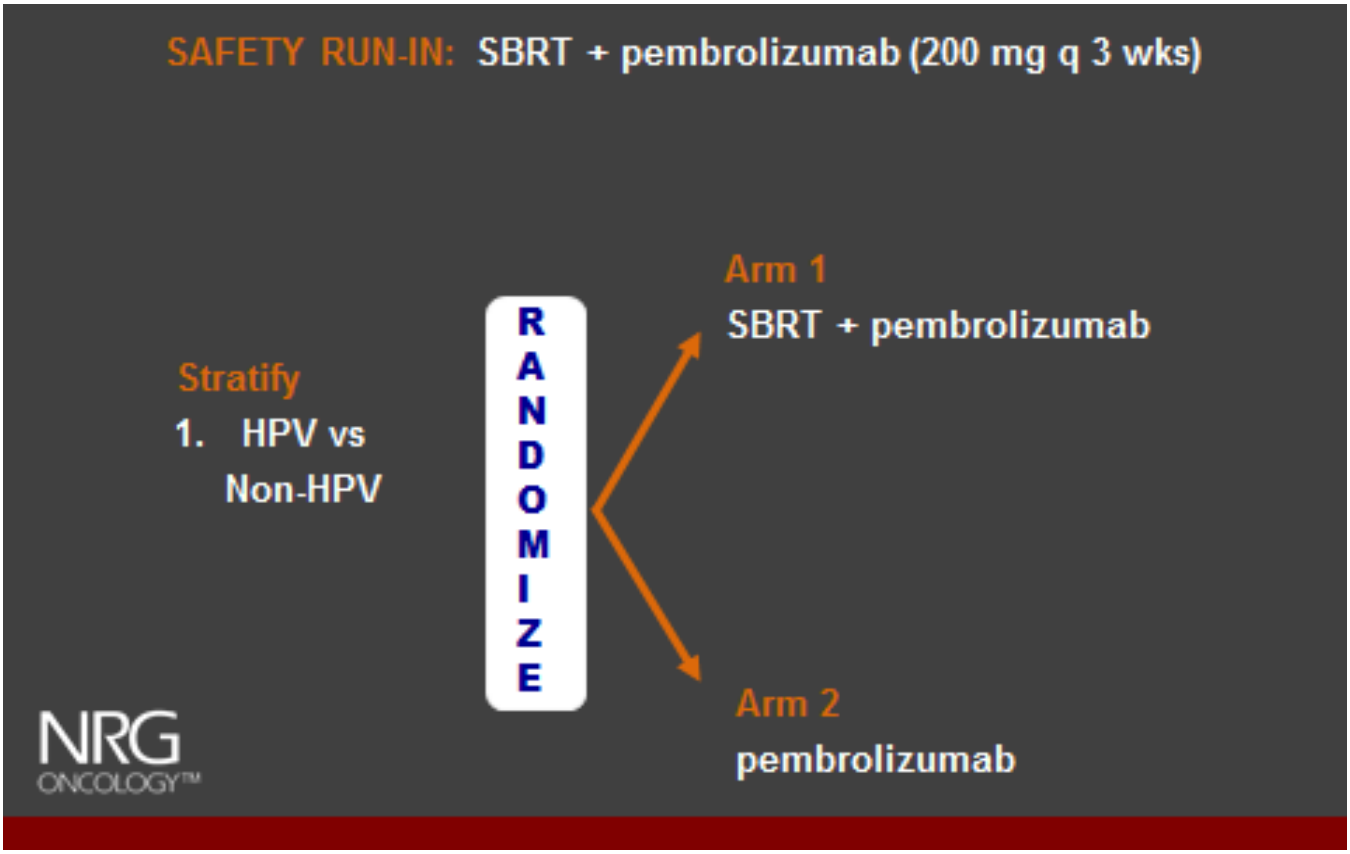
Continue treatment until disease progression; patients with documented progression but clinically stable may continue therapy after communication with ECOG – ACRIN

* Cetuximab (400 mg/m2 loading dose, 250 mg/m2) days 1, 8, 15, 22

** Urelumab (anti-CD137 mAb) (0.3 mg/kg) on day 2

*** Nivolumab (anti-PD1 mAb) (2 mg/kg) on day 2, 16

2. A Randomized Phase II Study of SBRT plus the Anti-PD-1 Antibody, Pembrolizumab, versus Pembrolizumab Alone for Oligo-Metastatic Head and Neck Carcinoma



Recommendation from Group 4 – Correlatives and Imaging

Tumor	PBMC	Sera	Imaging
IHC: CD8, CD8, CD45RO, CD4/FOXP3, PDL-1 (co stain on Macs). COMBINE OTHER TARGETED AGENT LIGAND ON LYMPHS/TUMOR; NK; Location of cells. Ki67 Fresh frozen: 1. RNA Seq (will include inhibitory/costim/exhaustion molecules targeted) 2. TCR diversity 3. (for TGFb inhibitor study: Phospho SMAD) Above assessments on all bx Biopsy needed for metastatic study (not on primary) **NUMBERS: FOR RNA, FOR MULTIPLEXED IF OR FFPE SLIDES*** **NODAL FNA: OK FOR mRNA? USEFUL FOR IF, TUMOR CELL PDL1 EXPRESSION?	Flow cytometry: 1. MDSC and Treg evaluations 2. T-cell activation panel (e.g. ICOS), memory subsets, PD-1 (any TRIAL DESIGN related costim/inhibitory molecules) 3. NK cell 4. TGFb: phospho-STAT (OR TARGET LIGAND PATHWAY ACTIVATION) Cytokine flow cytometry: 1. HPV+: 86/7 peptide pools (CD4/8, Type I/II cytokines (ICS) POLYFUNCTIONAL). Control: CEF 2. Non-HPV: common Ag peptide pools (e.g. p53, survivin; CD4/8, Type I/II cytokines (ICS) POLYFUNCTIONAL). Control: CEF SNP analysis (from PBMC gDNA)	Multiplex cytokine analysis (for trial of comparison of agents only); inflammatory molecules (esp. for IRX). POSSIBLE MEASURE OF TOXICITY? Antibody array at two time points (pre-last post) for epitope spreading.	Anti-PD-1 "window" study: PET-FDG/CT pre and after 4 week induction (predictor of early response via SUV measurements) (NO CURRENT TECHNOLOGY FOR IMMUNE ASSESSMENT VIA IMAGING)

Assume ALC obtained pre/during/post in clinical labs

Additional Consideration: stool samples and oral swabs for microbiome studies

ACTION PLANS:

CTPM Co-Chairs, the HNSC Co-Chairs and NCI staff will follow up with NRG and ECOG-ACRIN disease Chairs to prioritize which trials should move forward in 2015-16.

The presenters and co-chairs will prepare a manuscript from the proceedings to be submitted to *Oral Oncology*