NCI Head and Neck Steering Committee
TP53 Mutated Head and Neck Cancer
Clinical Trials Planning Meeting
January 21-22, 2021 (Virtual)
National Cancer Institute
Rockville, MD

Co-Chairs: Barbara Burtness, M.D., Christine Chung, M.D., Curtis Pickering, Ph.D., Shakun Malik, M.D.

Introduction/ Meeting Description- The Head and Neck Cancer Steering Committee received a proposal for a Clinical Trials Planning Meeting on *TP53* Mutated Head and Neck Cancer. This was approved by the Head and Neck Steering Committee in June 2019 and approved by the NCI in October 2019. The Core Planning Team began meeting in November 2019 to set the agenda, identify speakers and to form breakout brainstorming groups that began bi-weekly meetings in the spring of 2020 and met right up to the week before the meeting.

Background/Importance of Research Topic/Disease/Limitations

- Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer type in the world, with 800,000 new diagnoses and 400,000 patient deaths per year [1].
- Patients with mutated *TP53* have been identified as having poor outcomes compared to those retaining wild type *TP53* in many cancers, including HNSCC [2].

Loss of *TP53* function is not only the single most common genetic event in cancer but is also linked with more aggressive disease and poorer patient outcomes in many cancers [3,4]. This is particularly relevant in cancers of the head and neck in which mutations of the *TP53* gene are associated with the worst outcomes. The Cancer Genome Atlas (TCGA) has reported a *TP53* mutation frequency of over 80% in the majority of patients who are diagnosed with HPV negative HNSCC, making this the single most frequent genetic event in this disease [4].

Meeting Objectives

- Develop clinical trials for patients that can be conducted within the NCTN, with *TP53* mutant HNSCC in locally advanced and metastatic recurrent disease with a focus on biomarkers and signal seeking trials that will improve survival and quality of life.

Meeting Summary

- Overview of the *TP53* Landscape to include:
    - Genomics and Informatics Update
    - Personalized Medicine: Basket Trials Involving Synthetic Lethality
    - *TP53* Directed Oncogenes vs. Targeting Tumor Suppressors
    - Therapeutic Agents Leveraging Synthetic Lethal Interactions: Mitotic Checkpoint Kinases, DNA Damage Sensing Mechanisms, and Aurora Kinases
    - Algorithms to determine functionally significant *TP53* mutations

- Role of Immunotherapy in Metastatic and Recurrent Disease
- Aspects of Mutated Cancers and Treatment Resistance in Minority Populations
- Wee 1 Inhibitors
- Industry Presentations on Genomic Markers and Novel Agents

During the second half of the meeting, CTPM Leaders engaged with the 3 breakout groups. The biomarker group had provided all the breakout groups with substantial information prior to the meeting, and their members integrated with the remaining 3 Breakout Groups at the meeting. Each breakout group had been tasked to develop 2-3 potential concepts that would be prioritized by the CTPM committee after an open discussion. As mentioned above, the breakout groups had met at least twice a month for 6 months prior to the meeting.

- Locally Advanced - Leaders: Ranee Mehra and Heath Skinner
- Recurrent-Metastatic Disease Leaders: Cristina Rodriguez and Hyunseok Kang
- Signal Seeking – Leaders: Nabil Saba and Elsa Flores

Anticipated Consensus & Recommendation Action(s)

There was a total of 5 concepts that were prioritized by the Executive Committee to move forward. ECOG-ACRIN and NRG Head and Neck Cancer Disease Committees will decide the order in which they will be fully developed.

Junior Investigators were invited to the meeting and will be taking the lead on at least two publications on the outcome of the meeting.

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.

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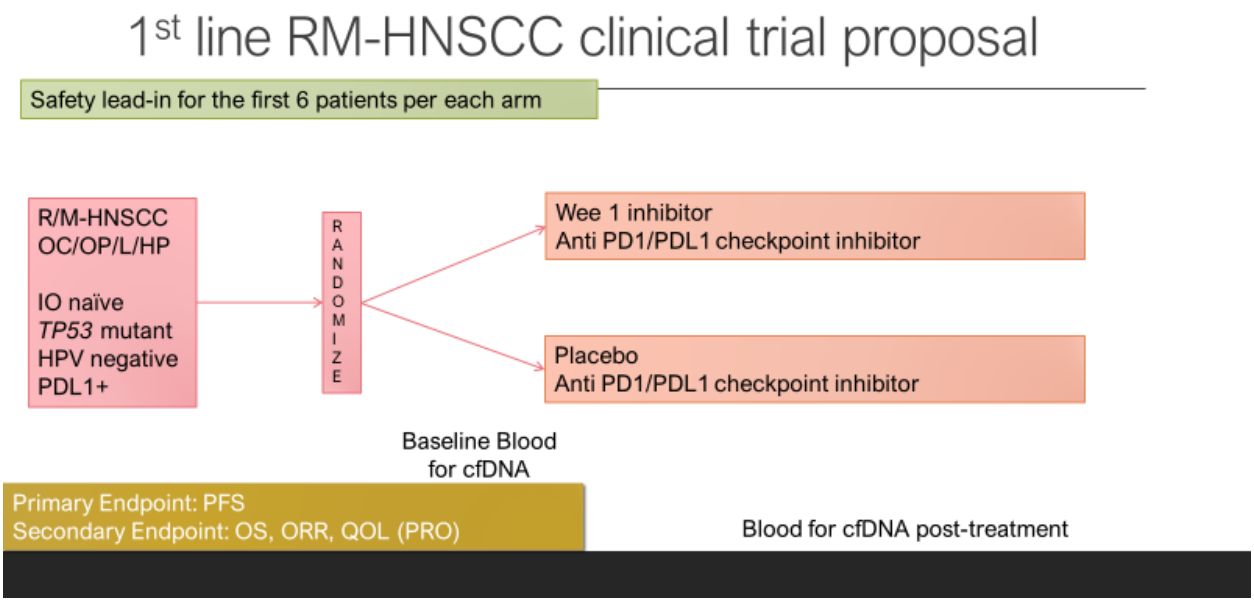
Proposals Prioritized for Development:



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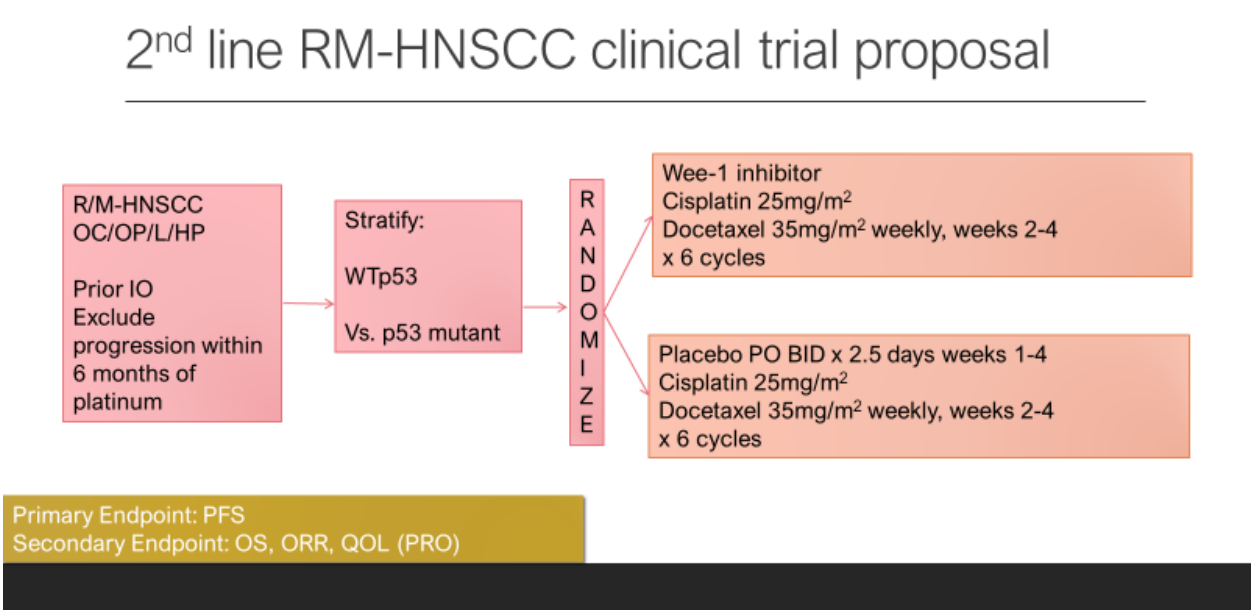
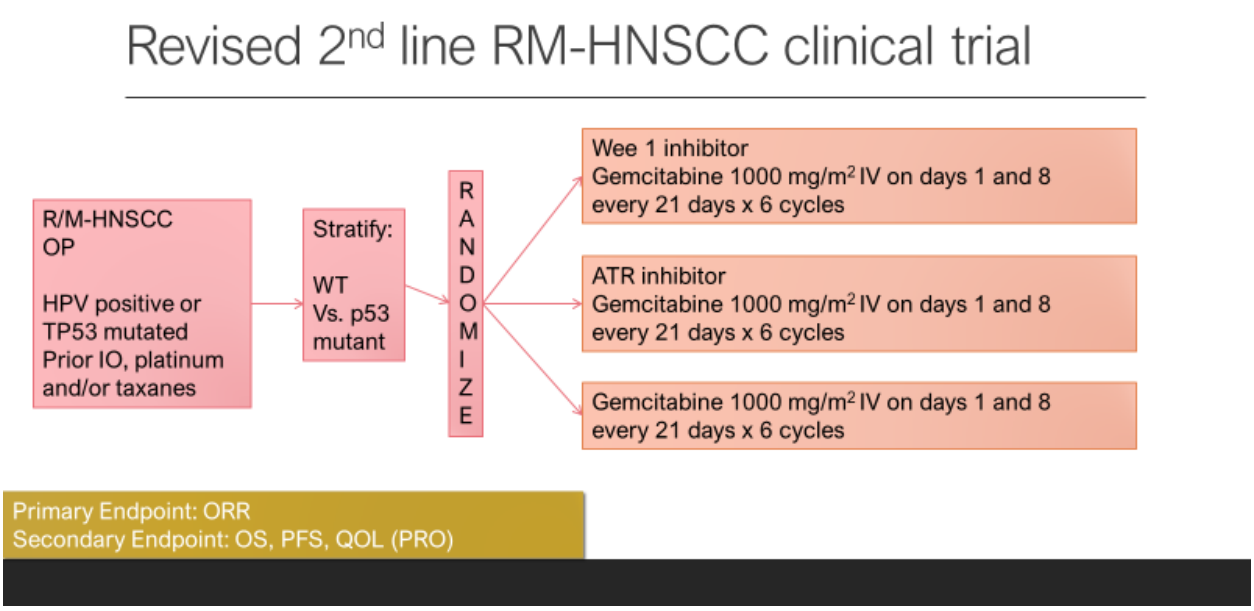
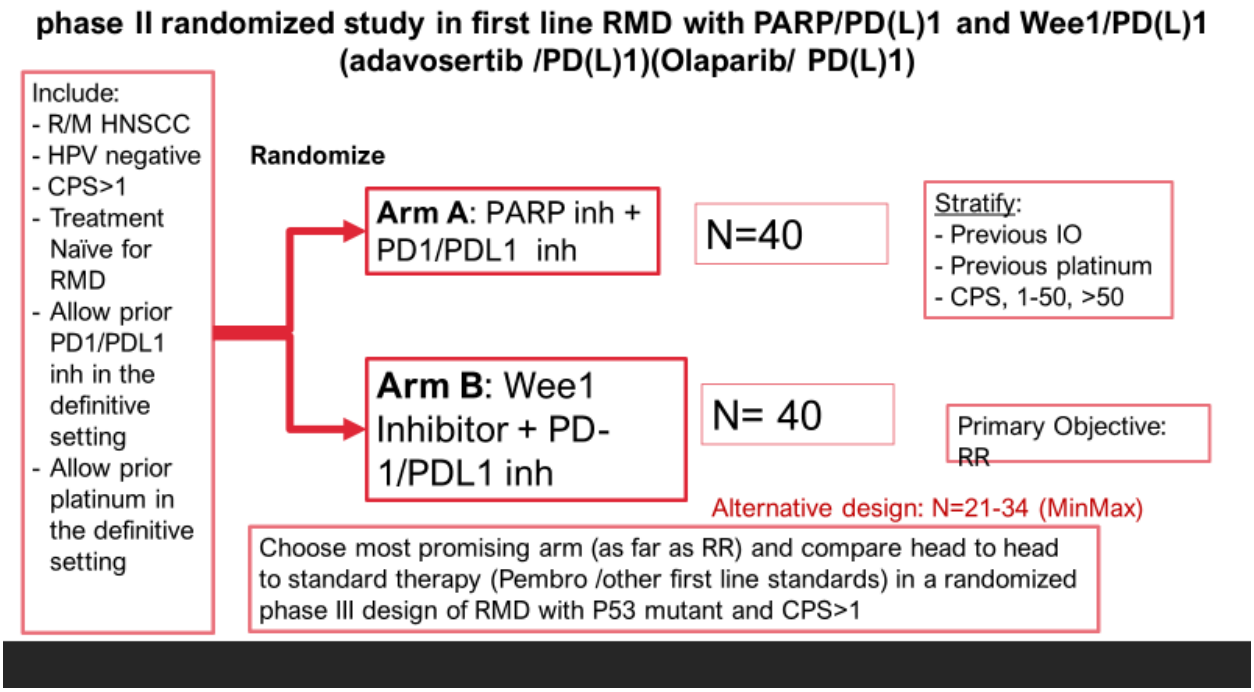
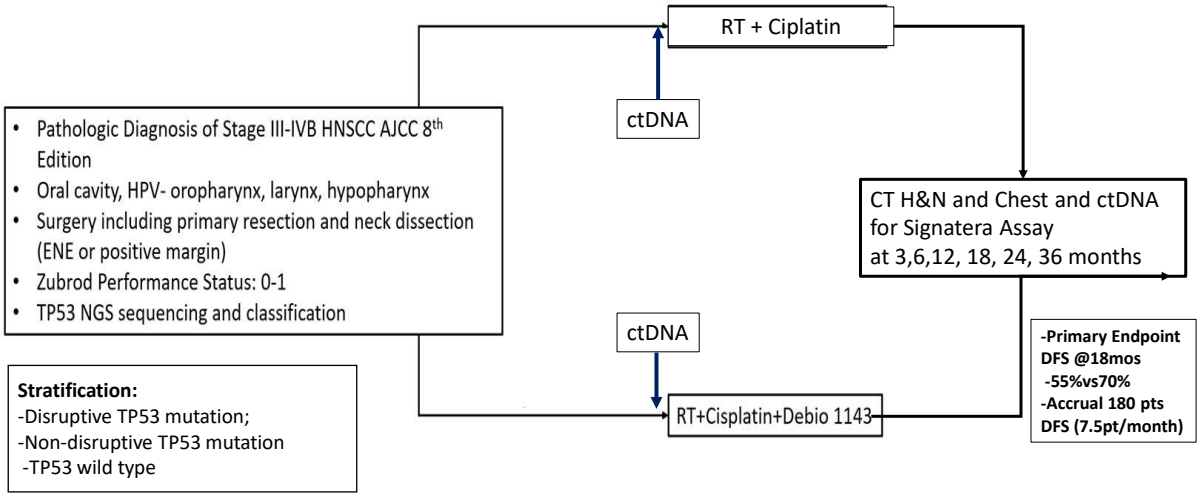



Revised 2nd line RM-HNSCC clinical trial
R/M-HNSCC
OP
HPV positive or
TP53 mutated
Prior IO, platinum
and/or taxanes
Stratify:
WT
Vs. p53
mutant
RANDOMIZE
Wee 1 inhibitor
Gemcitabine 1000 mg/m2 IV on days 1 and 8
every 21 days x 6 cycles
ATR inhibitor
Gemcitabine 1000 mg/m2 IV on days 1 and 8
every 21 days x 6 cycles
Gemcitabine 1000 mg/m2 IV on days 1 and 8
every 21 days x 6 cycles
Primary Endpoint: ORR
Secondary Endpoint: OS, PFS, QOL (PRO)


phase II randomized study in first line RMD with PARP/PD(L)1 and Wee1/PD(L)1 (adavosertib /PD(L)1)(Olaparib/ PD(L)1)
Include:
- R/M HNSCC
- HPV negative
- CPS>1
- Treatment Naïve for RMD
- Allow prior PD1/PDL1 inh in the definitive setting
- Allow prior platinum in the definitive setting
Randomize
Arm A: PARP inh + PD1/PDL1 inh
N=40
Stratify:
- Previous IO
- Previous platinum
- CPS, 1-50, >50
Arm B: Wee1 Inhibitor + PD-1/PDL1 inh
N= 40
Primary Objective: RR
Alternative design: N=21-34 (MinMax)
Choose most promising arm (as far as RR) and compare head to head to standard therapy (Pembro /other first line standards) in a randomized phase III design of RMD with P53 mutant and CPS>1

Randomized trial of adjuvant radiation therapy with molecularly targeted chemotherapy in pathologic high-risk, HPV-negative head and neck cancer



Suggested Biomarkers

Predictive biomarkers:
- (WES, RNA seq, HRD score) - hypothesis: p53 mutation status is associated with RR- detect p53 by WES RNA seq , IHC
- Pre-treatment HRD score- (correlates with benefit to PARP inh)

Monitoring for response/relapse:
- Ct-DNA even though mainly in virally mediated HNCA -exploratory biomarker for prediction of response (NCI/Natera ?) – hypothesis: ct-DNA predictive of response/resistance /relapse

Stratification biomarker:
- EAP53 /Poeta – (IHC)

Exploratory and profiling:
- Spatial genomics (Nano string digital special profiling) – (depends on tissue extent)

Integral biomarker:
- PDL1 by CPS score, HPV /p16 status for OPSCC

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References:

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2. https://www.sciencedirect.com/science/article/pii/S0304383520301014
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Names of Attendees at Meeting & their Affiliation

Doug Adkins, M.D.	Washington University
Clint Allen, M.D.	National Institutes of Health
Julie Bauman, M.D., MPH	University of Arizona
Barbara Burtness, M.D.	Yale University
Zhong Chen, M.D., Ph.D.	National Institute Dental Cranial Research
Christine Chung, M.D.	Moffit Cancer Center
Malgorzata Dominiewska, DVM	Astra Zeneca
Deborah Doroshow, M.D., Ph.D.	Tisch Cancer Institute
Anne Marie Egloff, Ph.D., MPH	Brigham & Women's Hospital
Carole Fakhry, M.D., MPH	University of Maryland
Robert Ferris, M.D., Ph.D.	Hillman Cancer Center, U of Pittsburgh
Elsa Flores, Ph.D.	Moffitt Cancer Center
James Ford, M.D.	Stanford University
Thomas Galloway, M.D.	Fox Chase Cancer Center
Jessica Geiger, M.D.	Cleveland Clinic
Robert Godin, M.D.	Astra Zeneca
Erica Golemis, Ph.D.	Fox Chase Cancer Center
D. Neil Hayes, M.D., MPH	Cancer Center
Leah Hubbard, Ph.D.	National Cancer Institute
Zain Husain, M.D.	University of Toronto
Deborah Jaffe, Ph.D.	National Cancer Institute
Hyunseok Kang, M.D.	University of California San Francisco
Rachel Karchin, Ph.D.	Johns Hopkins University
Tiffany Katz, Ph.D.	Natera
Randy Kimple, M.D., Ph.D.	University of Wisconsin
Charles Kunos, M.D., Ph.D.	National Cancer Institute
Quynh Thu Le, M.D.	Stanford University
Rom Leidner, M.D.	Providence Cancer Institute
Alice Li, M.D.	Kaiser Permanente
Guillermina Lozano, M.D.	MD Anderson Cancer Center
Gregory Lubiniecki, M.D.	Merck
Jean M. Lynn, MPH, RN	National Cancer Institute
Shakun Malik, M.D.	National Cancer Institute
Ranee Mehra, M.D.	University of Maryland
Luc Morris, M.D.	Memorial Sloan Kettering Cancer Center
Jeffrey Myers, M.D., Ph.D.	MD Anderson Cancer Center

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Thomas Myers, M.D.	Vitrac Pharmaceuticals
Cheri-Ann Nathan, M.D.	Louisiana State University
Giovanni Nitti, Ph.D.	Astra Zeneca
Brian O'Sullivan, M.D.	Princess Margaret Cancer Centre
Kym Pagel, Ph.D.	Johns Hopkins University
Linda Paradiso, DVM	Vitrac Pharmaceuticals
Curtis Pickering, Ph.D.	MD Anderson Cancer Center
Richard Piekarz, M.D., Ph.D.	National Cancer Institute
Mei Polley, Ph.D.	University of Chicago
Camille Ragin, Ph.D., MPH	Fox Chase Cancer Center
Lovett Evan Reddick, Ph.D.	Astra Zeneca
Cristina Rodriguez, M.D.	University of Washington
Angel Rodriguez, M.D.	Natera
Dario Ruscica, M.D.	Astra Zeneca
Nabil Saba, M.D.	Emory University
Elena Schwartz, Ph.D.	National Cancer Institute
Geoffrey Shapiro, M.D., Ph.D.	Dana Farber Cancer Institute
David Sher, M.D., MPH	UT Southwestern
Jeffery Shoop	Trials Patient
Heath Skinner, M.D. Ph.D.	University of Pittsburgh
Cheryl Solomon, MS	Emmes Corporation
Ramona Swaby, M.D.	Merck
Paul Swiecicki, M.D.	University of Michigan
Aik Choon Tan, Ph.D.	Moffit Cancer Center
Ravi Uppaluri, M.D., Ph.D.	Dana Farber Cancer Center
Chiayeng Wang, Ph.D.	National Cancer Institute
Stuart Wong, M.D.	Medical College of Wisconsin
Timothy Yap, M.D., Ph.D.	MD Anderson Cancer Center
Wendell Yarbrough, M.D.	University of North Carolina
Sue Yom, M.D., Ph.D.	University of California San Francisco
Zhiwei Zhang, Ph.D.	National Cancer Institute