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.
Proposals Prioritized for Development:

1st line RM-HNSCC clinical trial proposal

Safety lead-in for the first 6 patients per each arm

R/M-HNSCC
CC/OP/L/HP
IO naïve
TP53 mutant
HPV negative
PDL1+

RANDOMIZE

Wee 1 inhibitor
Anti PD1/PDL1 checkpoint inhibitor

Placebo
Anti PD1/PDL1 checkpoint inhibitor

Baseline Blood
for cfDNA

Primary Endpoint: PFS
Secondary Endpoint: OS, ORR, QOL (PRO)

Blood for cfDNA post-treatment
2nd line RM-HNSCC clinical trial proposal

R/M-HNSCC
OC/OP/L/HP
Prior IO
Exclude progression within 6 months of platinum

Stratify:
WTp53
Vs. p53 mutant

Randomize

Wee-1 inhibitor
Cisplatin 25mg/m²
Docetaxel 35mg/m² weekly, weeks 2-4 x 6 cycles

Placebo PO BID x 2.5 days weeks 1-4
Cisplatin 25mg/m²
Docetaxel 35mg/m² weekly, weeks 2-4 x 6 cycles

Primary Endpoint: PFS
Secondary Endpoint: OS, ORR, QOL (PRO)
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

- **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 Naive 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

Arm B: Wee1 Inhibitor + PD-1/PDL1 inh
N= 40

Stratify:
- Previous IO
- Previous platinum
- CPS, 1-50, >50

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

- Pathologic Diagnosis of Stage III-IVB HNSCC AJCC 8th Edition
- Oral cavity, HPV- oropharynx, larynx, hypopharynx
- Surgery including primary resection and neck dissection (ENE or positive margin)
- Zubrod Performance Status: 0-1
- TP53 NGS sequencing and classification

**Stratification:**
- Disruptive TP53 mutation;
- Non-disruptive TP53 mutation
- TP53 wild type

- Primary Endpoint
  - DFS @ 18mos
  - 55% vs 70%
  - Accrual 180 pts
  - DFS (7.5pt/month)
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 7) - 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

References:


<table>
<thead>
<tr>
<th>Names of Attendees at Meeting &amp; their Affiliation</th>
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<tbody>
<tr>
<td>Doug Adkins, M.D.</td>
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<td>Clint Allen, M.D.</td>
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<td>Julie Bauman, M.D., MPH</td>
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<td>Barbara Burtner, M.D.</td>
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<td>Zhong Chen, M.D., Ph.D.</td>
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<td>Christine Chung, M.D.</td>
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<td>Malgorzata Dominiewska, DVM</td>
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<td>Deborah Doroshow, M.D., Ph.D.</td>
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<td>Anne Marie Egloff, Ph.D., MPH</td>
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<td>Carole Fakhry, M.D., MPH</td>
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<td>Robert Ferris, M.D., Ph.D.</td>
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<td>Elsa Flores, Ph.D.</td>
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<td>James Ford, M.D.</td>
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<td>Thomas Galloway, M.D.</td>
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<td>Jessica Geiger, M.D.</td>
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<td>Robert Godin, M.D.</td>
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<td>Erica Golemis, Ph.D.</td>
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<td>Deborah Jaffe, Ph.D.</td>
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<td>Hyunseok Kang, M.D.</td>
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<td>Rachel Karchin, Ph.D.</td>
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<td>Tiffany Katz, Ph.D.</td>
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<td>Randy Kimple, M.D., Ph.D.</td>
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<td>Charles Kunos, M.D., Ph.D.</td>
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<td>Quynh Thu Le, M.D.</td>
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<td>Rom Leidner, M.D.</td>
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<td>Alice Li, M.D.</td>
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<td>Guillermina Lozano, M.D.</td>
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<td>Gregory Lubiniecki, M.D.</td>
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<td>Jean M. Lynn, MPH, RN</td>
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<td>Shakun Malik, M.D.</td>
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<td>Ranee Mehra, M.D.</td>
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<td>Luc Morris, M.D.</td>
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<td>Jeffrey Myers, M.D., Ph.D.</td>
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TP53 Mutated Head and Neck Cancer
Clinical Trials Planning Meeting
January 21-22, 2021 (Virtual)
National Cancer Institute
Rockville, MD
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