Clinical Trial Strategies and Priorities

Ezra E. W. Cohen
Treatment Overview

- Early stage (I, II): single modality – RT or surgery
  - 80-90% long-term survival
- Advanced stage (III, IVA, IVB): multi-modality therapy – surgery/RT/chemotherapy
  - 50% long term survival
- Recurrent/Metastasis
  - 15% can be salvaged (surgery, re-RT)
  - Palliative systemic therapy
NCI Clinical Trials Planning Meeting: Integrating Immunotherapy into Clinical Trials in Head and Neck Cancer

November 9-10, 2014

Update to the Head and Neck Steering Committee

May 30, 2015

CTPM Co-Chairs: Julie E. Bauman, MD, MPH
Ezra Cohen, MD
Robert Ferris, MD, PhD
CTPM Goals and Objective Outcomes

- Design three priority NCTN phase II or III trials to rationally integrate immunotherapy into HNSCC in the following disease settings:
  - PULA HPV (+)
  - PULA HPV (-)
  - Recurrent/Metastatic
- Explore unique endpoints and study design issues likely to be encountered in HNSCC immunotherapy trials
- Biomarkers of immunotherapy response: discovery and validation
Background:
HNSCC is an immunosuppressive disease

- Tumor-permissive cytokine profile
  - ↑ STAT3 cytokines: TGF-β, IL-6, IL-10
  - ↓ STAT1 cytokines: IFN-γ
- Quantitative and qualitative lymphocyte deficiencies
  - ↓ Absolute lymphocyte count
  - Spontaneous apoptosis of lymphocytes
- Anergic T cells
  - ↑ Co-inhibitory receptors: CTLA-4, PD-1
  - ↓ Co-stimulatory receptors: CD137, OX40
Rationale to focus on immunotherapy in HNSCC: two distinct etiologies

**HPV(-) Carcinogen-induced:**
- Overexpression or selective expression of tumor antigens: MUC-1, EGFR, the RAGE and GAGE families, NY-ESO-1, CEA and others
- Heavy mutation load

**HPV(+) Virally-induced:**
- Unique and specific tumor antigens: E6 and E7 oncoproteins
- Opportunity for antigen-specific targeting
The Immune Synapse

Adapted from Bauman JE and Ferris RL. Cancer 2013.
Pipeline Immunotherapies: Represented at the CTPM by CTEP and Industry

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enhancing ADCC</strong></td>
<td></td>
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<tr>
<td>IL-12 (NCI)</td>
<td>Cytokine agonist of NK cell activation</td>
</tr>
<tr>
<td>IL-15 (NCI)</td>
<td>Cytokine agonist of NK cell activation</td>
</tr>
<tr>
<td>VTX-2337</td>
<td>TLR 8 agonist; enhanced DC activation and IL-12 secretion</td>
</tr>
<tr>
<td>Liritumab (BMS)</td>
<td>Anti-Killer Inhibitor Receptor (KIR) mAb</td>
</tr>
<tr>
<td>1-7F9 (Innate)</td>
<td>Anti-KIR mAb</td>
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<tr>
<td><strong>Targeting Immunosuppressive Cytokines</strong></td>
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<tr>
<td>Siltuximab</td>
<td>Anti-IL-6 mAb</td>
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<tr>
<td>CAT-192</td>
<td>Anti-TGF-β mAb</td>
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<tr>
<td><strong>T cell Co-stimulatory Agonists</strong></td>
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<tr>
<td>CP-870,893 (Pfizer)</td>
<td>CD40 agonist mAb</td>
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<tr>
<td>OX40 mAb (AgonOx, Providence Health)</td>
<td>OX40 agonist mAb</td>
</tr>
<tr>
<td>Urelumab (BMS)</td>
<td>CD137 agonist mAb</td>
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<tr>
<td>PF-05082566 (Pfizer)</td>
<td>CD137 agonist mAb</td>
</tr>
<tr>
<td>IMP321 (Immunepep)</td>
<td>Recombinant soluble dimeric LAG3</td>
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<td><strong>T cell Immune Checkpoint Inhibitors</strong></td>
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<tr>
<td>Ipilimumab (BMS)</td>
<td>Anti-CTLA4</td>
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<td>Tremelimumab (Pfizer, Medimmune)</td>
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<td>Nivolumab (BMS)</td>
<td>Anti-PD1 mAb</td>
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<td>Pembrolizumab (Merck)</td>
<td>Anti-PD1 mAb</td>
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<td>CT-011 (Curetech)</td>
<td>Anti-PDL1 mAb</td>
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<tr>
<td>MEDI-4736 (Medimmune)</td>
<td>Anti-PDL1 mAb</td>
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<tr>
<td>MPDL3280A (Genentech)</td>
<td>Anti-PDL1 mAb</td>
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<tr>
<td>MSB0010718C (EMD Serono)</td>
<td>Anti-PDL1 mAb</td>
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<tr>
<td>AUNP12 (peptide) (Pierre Fabre/Aurigene)</td>
<td>Anti-PDL1 peptide</td>
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<td>BMS-986016 (BMS)</td>
<td>Anti-LAG3 mAb</td>
</tr>
<tr>
<td>INCB024360 (Incyte)</td>
<td>Orally available inhibitor of indoleamine 2,3-dioxygenase (IDO1)</td>
</tr>
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</table>
CTPM Agenda: Educational Session (Open)

- **Overview of HNSCC: State of Knowledge**
  - Current Status of HNSCC Therapeutic Strategies (*Cohen*)
  - HNSCC Immunology and Immune Escape (*Ferris*)
  - Role of Immunity in Response to Chemo/Radiotherapy (*Hodge*)

- **Clinically Available Immunotherapeutic Targets**
  - Co-Inhibitory Receptor Antagonists (CTLA-4, PD-1) (*Gajewski*)
  - Cytokine combinations & antagonists (IL-12, -15, anti-VEGF, anti-TGF-beta, JAK/STAT inhibitors) (*Carson*)
  - Co-stimulatory/Inflammatory Agonists (CD137, TLR3/7/8 agonists) (*Fox*)
  - Vaccines for HPV and non-HPV disease (*Gillison*)
  - Unique aspects of Toxicity and Response Assessment to Immunotherapy (*Bauman*)
CTPM Agenda: Breakout Groups (Closed)

- **Working Group 1: HPV(+) PULA**
  - Robert Ferris, MD, PhD and Maura Gillison, MD

- **Working Group 2: HPV(-) PULA**
  - Julie Bauman, MD, MPH and David Raben, MD

- **Working Group 3: Recurrent/Metastatic**
  - Ezra Cohen, MD and Scott Strome, MD

- **Working Group 4: Monitoring for Efficacy in Immunotherapeutic Trials – Specimen Analyses, Imaging, Correlative Immune Monitoring**
  - Lisa Butterfield, PhD and Nora Disis, MD
CTPM Breakout Group 1
HPV(+) PULA Disease

On behalf of: David Adelstein, Bryan Bell, David Brizel, Anthony Cmelak, Dimitri Colevas, Adam Dicker, Avi Eisbruch, Robert L. Ferris, Maura Gillison, Young Kim, Loren Mell, Brian O'Sullivan, Harry Quon, Ralph Weichselbaum, Greg Wolf, Ed Zhang
Proposal 1:
“Window” anti- PD-1/PD-L1 biomarker study followed by universal definitive CRT +/- adjuvant anti-PD1 in high-risk HPV+ oropharynx cancer patients (T4 or N3; ? Smokers only)

Baseline Biomarkers: Immunoscore, inflamed phenotype, PD-L1, CT scan

4 wk. window
- HPV vaccine
- Anti-PD1/ PD-L1
- Anti-PD1/ PD-L1 + Vaccine
- Biopsy for biomarker panel CT scan

Randomize

70 Gy + DDP + Vaccine
70 Gy + DDP + anti-PD-1
70 Gy + DDP + anti-PD-1 + Vaccine

*b anti-PD1 given as concurrent or adjuvant – 2 arms?

* blood/tumor collection

Primary clinical endpoint: 3-year event-free survival
Secondary endpoints: Distant metastatic control, locoregional control, O.S.
10% improvement in primary endpoint; alpha .10; power 80%
Anticipated accrual 6 patients/month
Table 1. Sample sizes and study time for DM control.

<table>
<thead>
<tr>
<th>Control rate</th>
<th>Accrual rate</th>
<th>Alpha</th>
<th>Power</th>
<th>3 year control rate (c)</th>
<th>3 year control rate</th>
<th>Difference</th>
<th>Hazard ratio</th>
<th>Sample size</th>
<th>Accrual time</th>
<th>Study time</th>
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<tbody>
<tr>
<td>O'Sullivan</td>
<td>6pts/month</td>
<td>0.15</td>
<td>80%</td>
<td>76%</td>
<td>85%</td>
<td>9%</td>
<td>0.592</td>
<td>200</td>
<td>3.7</td>
<td>6.0</td>
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<td>76%</td>
<td>88%</td>
<td>12%</td>
<td>0.466</td>
<td>150</td>
<td>2.8</td>
<td>4.2</td>
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<td>RTOG*</td>
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<td>4.3</td>
</tr>
</tbody>
</table>

*RTOG 0129 and 0522 combined (n=216 patients, 33 events, p16-positive oropharynx cancer, T4 and/or N2c-N3, distant control censored at last follow-up or death).

Note: changes from rows 1-4 to 6-9 are accrual is doubled; changes from rows 6-9 to 11-14 are alpha is reduced to 0.1.
CTPM Breakout Group 2  
HPV(-) PULA Disease


Randomized, Phase II Study of Adjuvant Cisplatin-Radiotherapy with or without Anti-PD-L1 Monoclonal Antibody in High Risk, HPV-negative Head and Neck Cancer with Window Correlatives
Schema 1

**HPV(-) PULA HNSCC**
- Clinically high risk HPV(-) oral cavity, pharynx, larynx
- Zubrod 0-1
- Planned for definitive surgery

# Stratify:
N0-2b vs. N2c-N3

**Tissue Biomarkers**: ★

**Blood Biomarkers**: ★★

**Eligibility (Clinical):**
- Stage IVa-IVb HPV(-) oral cavity, pharynx, larynx
- Zubrod 0-1
- ECOG 0-1
- Planned for definitive surgery

**Primary Endpoint: 2-year PFS**

**Secondary Endpoints:**
- Toxicity (acute, late)
- Tissue and blood biomarkers (baseline, delta) and relationship to 2-year PFS, LRC, distant metastases, toxicity
Eligibility (Clinical):
• Stage III-IVb HPV(-) oral cavity, pharynx, larynx
  • T3-4, any N (except T3N0 larynx)
  • T1-2, N2-3
  • Oral cavity, any T, level IV or V node
• ECOG 0-1
• Planned for definitive surgery

Primary Endpoint: 1-year PFS
Secondary Endpoints:
• Toxicity (acute, late)
• Tissue and blood biomarkers (baseline, delta) and relationship to 1-year PFS, LRC, distant metastases, toxicity
Eligibility Refinement – Developing a Clinical Algorithm of High Risk

• Hypopharynx  T1-2N1-3 or T3-4N0-3
• Larynx  T1-2N2a-3 or T3-4N0-3
• Oral cavity  T1-2N2a-3 or T3-4N0-3
• p16-negative OP  T1-2N2a-3 or T3-4N0-3

• Analysis of RTOG 0234:
  – 81 of 102 clinically selected patients have ECE or positive margin
  – 2-year DFS for this subset is 51.5%
  – Projected monthly accrual rate for this subset is 3.8 pts/month
Primary Objective(s) and Brief Statistical Design

• **Primary Objective:** To evaluate the efficacy of adjuvant CRT and anti-PD-L1 mAb, as compared to standard CRT, in patients with high risk HNSCC who have undergone primary surgery (primary endpoint 2-yr DFS)

• **Statistical Considerations:**
  - Type I Error ($\alpha$) = 0.15
  - Power 80%
  - Hazard Ratio 0.55
  - $N = 62$ evaluable patients (70 to account for ineligibility)
  - Study duration: 5 years (1.5 years accrual time; intended to accrue while RTOG 1216 is paused for interim analysis)
CTPM Breakout Group 3
Recurrent/Metastatic Disease

• On behalf of: Laura Chow, Christine Chung, Ezra Cohen, Marka Crittenden, Antonio Jimeno, Holbrook Kohrt, John Lee, Shakun Malik, Brian Nussenbaum, Drew Ridge, Tanguy Seiwert, Andrew Sikora, Scott Strome, Jeremy Taylor, Stuart Wong
A Randomized Phase II Study of SBRT plus the Anti-PD1 mAb Pembrolizumab, vs. Pembrolizumab Alone for Oligometastatic HNC

Allen Chen MD, Study Chair
Nooshin Hashemi Sadraei, MD, Medical Oncology Co-Chair
Christine Chung, MD, Translational Co-Chair
John Sunwoo MD, Surgery Co-Chair

• Hypothesis:
  – Hypofractionated doses of radiation in SBRT enhance the immunologic effects of anti-PD1 therapy in HNSCC
SCHEMA

SAFETY RUN-IN: SBRT + pembrolizumab (200 mg q 3 wks)

Stratify
1. HPV vs Non-HPV

Arm 1
SBRT + pembrolizumab

Arm 2
pembrolizumab
Treatment Plan

- **SBRT:** 7 Gy x 5 fractions over 11 or 12 days, (total dose of 35 Gy)
  - One or two lesions may be treated, but at least one lesion must be untreated and evaluable in two dimensions

- **Pembrolizumab:** 200 mg flat dose IV q 3 week
  - Based upon PK relative to mg/kg dosing and q 2 week dosing
  - Starting prior to RT
  - Duration: 12 months
Objectives and Statistical Considerations

- **Primary:**
  - PFS at one year

- **Secondary:**
  - OS at one year
  - In- and out-of field response
  - Toxicity

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>1 yr difference</th>
<th>Hazard ratio</th>
<th>alpha</th>
<th>power</th>
<th>Sample size</th>
<th>events</th>
<th>Accrual time</th>
<th>Study time</th>
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<tr>
<td>PFS</td>
<td>15%- &gt;30%</td>
<td>0.635</td>
<td>10%</td>
<td>85%</td>
<td>122</td>
<td>104</td>
<td>3.4</td>
<td>3.9</td>
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</table>

85% power, 10% error
Phase II RCT of Weekly Cetuximab plus anti-CD137 mAb, anti-PD1 mAb, or the Triplet Combination in Recurrent/Metastatic HNSCC

**Screening**
- *2nd line, platinum refractory or not appropriate*
- *cetuximab naïve in RM setting*

**Treatment Period:** up to 1 year of therapy with every 3-week cycles

**DLT Assessment Window:** Day 0 – Day 43

**One Cycle:** D0 – D21

**Eligibility:**
- **PS required for stratification of 1:1:1 randomization**
- **p16 status evaluated for post-hoc analysis of effect**

**Co-Primary Endpoints:** Safety and 6-month PFS

*confirmed progression of disease. Patients with confirmed PD, otherwise clinically stable, may continue on combination therapy in discussion with the medical monitor. Patients with confirmed PD, not clinically stable, requiring alternative therapy should discontinue study drug.
CTPM Breakout Group 4: Monitoring for Efficacy in Immunotherapeutic Trials – Specimen Analyses, Imaging, Correlative Immune Monitoring

- On behalf of: Lisa Butterfield, Nora Disis, Bernie Fox, Franco Marincola, Mary Naimoli, Jeffrey Moyer, Sara Pai, Elad Sharon, James Stapleton, Howard Streicher, Walter Urba, Xiao-Jing Wang
<table>
<thead>
<tr>
<th>Tumor</th>
<th>PBMC</th>
<th>Sera</th>
<th>Imaging</th>
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<tr>
<td>IHC:</td>
<td>Flow cytometry:</td>
<td>Multiplex cytokine analysis</td>
<td>Anti-PD-1 “window” study:</td>
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<tr>
<td>CD3, CD8, CD45RO, CD4/FOXP3, PDL-1 (co stain on Macs). <strong>COMBINE OTHER TARGETED AGENT LIGAND ON LYMPHS/TUMOR; NK, Location of cells. Ki67</strong></td>
<td>1. MDSC and Treg evaluations</td>
<td>(for trial of comparison of agents only); inflammatory molecules (esp. for IRX).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. T-cell activation panel (e.g. ICOS), memory subsets, PD-1 (any TRIAL DESIGN related costim/inhibitory molecules)</td>
<td><strong>POSSIBLE MEASURE OF TOXICITY?</strong></td>
<td>(NO CURRENT TECHNOLOGY FOR IMMUNE ASSESSMENT VIA IMAGING)</td>
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<tr>
<td>Fresh frozen:</td>
<td>3. NK cell</td>
<td>Antibody array at two time points (pre-last post) for epitope spreading.</td>
<td></td>
</tr>
<tr>
<td>1. RNA Seq (will include inhibitory/costim/exhaustion molecules targeted)</td>
<td>4. TGFb: phospho-STAT (OR TARGET LIGAND PATHWAY ACTIVATION)</td>
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<td></td>
</tr>
<tr>
<td>2. TCR diversity</td>
<td>Cytokine flow cytometry:</td>
<td></td>
<td></td>
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<tr>
<td>3. (for TGFb inhibitor study: Phospho SMAD)</td>
<td>1. HPV+:, E6/7 peptide pools (CD4/8, Type I/II cytokines (ICS) POLYFUNCTIONAL). Control: CEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above assessments on all bx</td>
<td>2. Non-HPV: common Ag peptide pools (e.g. p53, survivin; CD4/8, Type I/II cytokines (ICS) POLYFUNCTIONAL). Control: CEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy needed for metastatic study (not on primary)</td>
<td>SNP analysis (from PBMC gDNA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NUMBERS: FOR RNA, FOR MULTIPLEXED IF OR #FFPE SLIDES***

**NODAL FNA: OK FOR mRNA? USEFUL FOR IF, TUMOR CELL PDL1 EXPRESSION?**

Assume ALC obtained pre/during/post in clinical labs

Additional Consideration: stool samples and oral swabs for microbiome studies
Outcomes: Trials Under Development in the NCTN

- Randomized Phase II Study of SBRT plus the anti-PD1 mAb Pembrolizumab vs. Pembrolizumab Alone for Oligometastatic HNC

- Randomized Phase II Study of Adjuvant Cisplatin-Radiotherapy with or without Anti-PD-1 mAb in High Risk, HPV-negative HNC with Window Correlatives

- Phase II RCT of Weekly Cetuximab plus anti-CD137 mAb, anti-PD1 mAb, or the Triplet Combination in Recurrent/Metastatic HNC
ONGOING INDUSTRY STUDIES
A Randomized, Double-Blind, Placebo-Controlled Study of Chemotherapy Plus Cetuximab in Combination with VTX-2337 in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Active8
Study Schema

175 patients with locally advanced or metastatic head/neck cancer
Primary endpoint: progression-free survival
CheckMate 141: Nivolumab vs. Investigator’s Choice in R/M HNSCC

Randomized, phase III trial of nivolumab vs. investigator’s choice in R/M HNSCC after relapse or progression within 6 months of platinum therapy¹,²

N=360

Key Eligibility Criteria
- R/M HNSCC (oral cavity, oropharynx, larynx, or hypopharynx)
- Progression on prior platinum therapy
- ECOG PS 0–1
- Documentation of p16+ or p16− to determine HPV status for oropharyngeal HNSCC
- No active CNS metastases

Start Date: May 2014
Estimated Study Completion Date: September 2017
Estimated Primary Completion Date: October 2016
Status: Recruiting
Study Director: Bristol-Myers Squibb

Nivolumab 3 mg/kg IV q2w

Methotrexate, or docetaxel, or cetuximab

Until progression or study drug discontinuation†

- Primary Outcome Measure: OS
- Secondary Outcome Measures: PFS, ORR
- Select Exploratory Outcome Measures: Safety, DOR, TTR, immune pharmacodynamics, biomarkers, PK, HRQoL

* Stratified by prior cetuximab treatment (yes vs no); † Treatment beyond progression option for nivolumab arm.

CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; HPV, human papillomavirus; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; R, randomized; QLQ, quality of life questionnaire; R, randomized; R/M, recurrent/metastatic; HNSCC, squamous cell carcinoma of the head and neck; TTR, time to response.

Recurrent/metastatic HNC 2nd line: HAWK

Figure 1  Overall study design

D4193C00001
Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) who have progressed after treatment with a platinum containing regimen for recurrent or metastatic disease. N=96

PD-L1 +ve

MEDI4736
Monotherapy
10mg/kg, IV, q2W

Objective disease progression
Primary endpoint: ORR

IV Intravenous; ORR Objective response rate; PD-L1+ Programmed cell death ligand-1 positive; q2w Every 2 weeks.

PI: Dan Zandberg
Recurrent/metastatic HNC 2nd line: CONDOR

Figure 1: Overall study design

Randomization to 3 arms according to HPV status and smoking status as follows:

- PD-L1−ve
  - D4193C00003
    - Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) who have progressed after treatment with a platinum containing regimen for recurrent or metastatic disease
    - N randomized: 240
    - Max N evaluable for primary endpoint (ORR): 208

2:1:1

- MEDI4736 + tremelimumab combo
  - N randomized: 120
  - N evaluable: 104

- MEDI4736 mono
  - N randomized: 60
  - N evaluable: 52

- Tremelimumab mono
  - N randomized: 60
  - N evaluable: 52

Objective Response Rate (evaluable patients) and Objective Disease Progression and Overall Survival (randomized patients)

PI: Lillian Siu
Recurrent/metastatic HNC 2\textsuperscript{nd} line: EAGLE
1st line treatment for recurrent HNSCC

**Target Population**
- Patients with recurrent or metastatic SCCHN
- No prior chemotherapy for recurrent/metastatic disease
- PS 0 to 1
- Excludes nasopharyngeal cancer
- Excludes prior immunotherapy

N = 628 patients

**Randomization stratified for:**
1. PD-L1 Status (~440 PD-L1-negative patients)
2. Tumor location
3. Smoking history

**Outcomes:**
- MEDI4736 + Tremelimumab N=314
- Cetuximab + Platinum* +5-Fluorouracil (SoC - EXTREME) N=157
- MEDI4736 monotherapy N=157

* Platinum: carboplatin or cisplatin

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Trial Design PN055

Eligibility
- Head & Neck Squamous Cell Carcinoma?

Open-Label MK-3475 (n=150)
- 200 mg Pembrolizumab (MK-3475) Q3W
- Discontinue Study Treatment?

Post Treatment
- Safety and Survival Follow-up

- Yes

Resistant to Platinum AND Cetuximab?

Yes

No

Stratification by:

1. ECOG status (0 vs 1)
2. HPV status# (positive vs negative)
3. PD-L1 status (strong positive* vs not)

Pembrolizumab 200mg Q3W

Investigator’s Choice from one of the following:
- Methotrexate
- Docetaxel
- Cetuximab

R = Randomization      PD = Progressive Disease      SFU = Survival Follow-up

#For oropharyngeal cancer only.
*Strong positive is defined as \( \geq 50\% \) PD-L1 testing by IHC. PD-L1 analysis will be blinded to both site and sponsor.
Stratification

1. Tumor PD-L1 (Strongly positive or not strongly positive)
   - 1st 600 enrolled all PD-L1
   - Then 180 strongly + PD-L1

2. HPV status\(^a\) (Positive or Negative)

3. ECOG status (0 or 1)

RAND\(\text{OMIZE}\)

Pembrolizumab (200 mg Q3W)

Pembrolizumab (200 mg Q3W) + Platinum\(^b\)
   - (Cisplatin - 100 mg/m\(^2\) Q3W or Carboplatin AUC 5 mg/ml/min Q3W) +
   - 5-FU \(^b\)
   - (1000 mg/m\(^2\)/d over 4 days Q3W)

Cetuximab
   - (400 mg/m\(^2\) initial then 250 mg/m\(^2\) QW) +
   - Platinum\(^b\)
   - (Cisplatin - 100 mg/m\(^2\) Q3W or Carboplatin AUC 5 mg/ml/min Q3W) +
   - 5-FU \(^b\)
   - (1000 mg/m\(^2\)/d over 4 days Q3W)

1:1:1

c. PD = Progressive disease
d. SFU = Survival follow-up

a. Local testing for subjects with oropharyngeal cancer

b. Maximum 6 cycles of platinum and 5-FU
CONCLUSIONS

• Many ongoing studies incorporating immunotherapeutic agents ongoing
  – Too many to list
• Current phase 3 trials likely to garner approval for PD1/PDL1 antibodies in near future
• Needs:
  – Think beyond PD1/PDL1
  – Develop biomarkers, especially predictive
  – Think beyond recurrent/metastatic disease